EFFECT OF DOBUTAMINE ON RENAL RESISTIVE INDEX IN SEPTIC SHOCK PATIENTS

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Dedicated

to

my Family

&

Teachers

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Dr. Mandava Venkata Sravani

ABBREVIATIONS

AKI: Acute Kidney Injury

ACCM: American College of Critical Care Medicine

BCE: Before Christ Era

CI: Cardiac Index

CI: Confidence Interval

CVP: Central Venous Pressure

DO2: Delivery of Oxygen

EF: Ejection Fraction

GCS: Glasgow Coma Scale

GEDI: Global End Diastolic Index

GFR: Glomerular Filtration Rate

HR: Heart Rate

ICU: Intensive Care Unit

IVC: Inferior Vena Cava

LFT: Liver Function Test

MAP: Mean Arterial Pressure

OR: Odds Ratio

PaO2: Partial Pressure of Oxygen

PLR: Passive Leg Raising

PPI: Peripheral Perfusion Index

PPV: Pulse Pressure Variation

qSOFA: quick Sequential Organ Failure Assessment

RAP: Right Atrial Pressure

RBF: Renal Blood Flow

RFT: Renal Function Test

ROC: Receiver Operating Characteristic

RRI: Renal Resistive Index

RRT: Renal Replacement Therapy

SOFA: Sequential organ failure assessment

SPV: Systolic Pressure Variation

SSC: Surviving Sepsis Campaign

SVI: Stroke Volume Index

SVRI: Stroke Volume Resistance Index

USA: United States of America

VO2: Volume of Oxygen Consumption

ABSTRACT

Introduction: Septic shock is diagnosed if there is persistent hypotension with MAP < 65mm Hg with serum lactate level >2 mmol/dl despite adequate initial fluid resuscitation. If hypotension persists after initial resuscitation, Nor-epinephrine is the first vasopressor of choice. Dobutamine is suggested in patients with evidence of persistent hypoperfusion despite adequate fluid resuscitation and vasopressor support. Kidney is the most common organ affected in sepsis. Renal Resistive Index (RRI) is a sonographic measurement of resistance to flow in intra-renal arteries which is used as a marker of renal perfusion.

Aim of Study: To evaluate the effect of dobutamine on Renal Resistive Index in septic shock patients.

Materials & Methods: In septic shock patients, following adequate resuscitation, if MAP< 65 mm Hg persists then nor- epinephrine was used as the first line vasopressor. After stabilization with MAP > 65 mm Hg, if signs of organ hypoperfusion persist then dobutamine infusion was started at 3µg/kg/min. The effect of dobutamine on vital parameters, lactate and RRI were monitored periodically over 48 hours.

Results: Majority of the patients were males (64%) with a mean age of 48.16±15 years. In our study, there was a significant decrease in heart rate and increase in MAP (p= 0.001) over 48 hours after starting dobutamine infusion. The dose of nor-epinephrine significantly increased initially after starting dobutamine. There was a significant decrease (p= 0.001) in lactate and RRI after starting dobutamine infusion. There was no significant correlation between serum lactate levels and RRI values over 48 hours. There was also no significant relationship between pre resuscitation RRI and prediction of AKI on day 3 of septic shock.

Conclusion: This study concludes that there was a significant decrease in RRI following dobutamine infusion which is a marker of renal perfusion. There was no significant correlation between RRI and serum lactate levels. There was also no relationship between pre resuscitation RRI in septic shock with development of AKI on day 3.

Key words: Septic shock, Renal resistive index, Dobutamine, Acute kidney injury

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INTRODUCTION

Sepsis is a clinical syndrome caused by host's response to infection and has got profound adverse physiological effects. Sepsis is believed to be one the leading cause of in-hospital mortality and morbidity in recent times.[1] The Third International Consensus Definitions of Sepsis and Septic Shock guidelines (Sepsis-3) defines "Sepsis as a life threatening organ dysfunction caused by dysregulated host response to infection" and septic shock as "subset of sepsis with circulatory and cellular/metabolic dysfunction associated with higher risk of mortality."[1,2,3]

Owing to the ambiguity and complexity of sepsis, it is extremely difficult to set concrete criteria for identifying it and forming definitive guidelines in the management of sepsis. However, there had always been an emphasis on early initiation of resuscitation and treatment of sepsis. This lead to the most important revision of Surviving Sepsis Campaign (SSC) bundle that the 3-hour and 6-hour bundles into a single "hour-1 bundle" in the SSC update 2018.[3,4]

SSC update 2018 recommends initiation of resuscitation and treatment, such as measuring lactate, obtaining blood cultures, administration of fluids and antibiotics and initiation of vasopressors to target MAP should be initiated within one hour. However, more than one hour may be required to complete resuscitation.[4]

The new Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic shock 2021 recommends early identification of sepsis and manage appropriately within the initial hours of sepsis to improve outcomes. These recommendation emphasis on the early and appropriate antibiotics, fluid resuscitation and vasopressor choice with slight changes from the previous guidelines.[5]

The guidelines recommend rapid administration of crystalloid at 30ml/kg in case of hypotension or if lactate is ≥2 mmol/l.[3,4] The American College of Critical Care Medicine (ACCM) recognize that a MAP of atleast 65 mm Hg is required to perfuse organs. If after

appropriate resuscitation the MAP does not improve to about 65 mm Hg it is recommended that vasopressors be initiated.[3,4,5]

Norepinephrine is recommended as the initial vasopressor as per SSC 2021 recommendations (Strong recommendation & low quality evidence). While there was an ambiguity in the choice of second vasopressors in previous guidelines, the latest guidelines suggest vasopressin as the second choice vasopressor to maintain a mean arterial pressure of >65 mm Hg (weak recommendation &moderate quality evidence). Despite norepinephrine and vasopressin if MAP is inadequate epinephrine should be considered (weak recommendation & low quality evidence). In patients with septic shock and cardiac dysfunction with persistent organ hypoperfusion and MAP<65 mm Hg despite adequate fluid resuscitation, either dobutamine should be added to norepinephrine or epinephrine alone should be used. (weak recommendation & low quality evidence).[5] The end point of the resuscitation is ultimately determined by the organ perfusion and the vasopressor's dosage should be titrated accordingly.[2]

Serum lactate is being used as a surrogate marker of organ perfusion in sepsis.[2,3] However serum lactate cannot be considered as a direct measure of organ perfusion, as it can be raised in other causes such as liver failure and high dose vasopressors.[2,6] This necessitates the need for alternative objective indicator of organ perfusion.[2,6] Patients with multiple co-morbid conditions including chronic illnesses (e.g., diabetes) and chronic organ dysfunction (e.g., liver or renal failure) and on catecholamine infusion can cause increase in lactate levels despite adequate organ perfusion.[2,5]

Acute kidney injury (AKI) is an important early marker of organ perfusion.[7] AKI is seen in 25% of sepsis patients in ICU.[7] Bedside ultrasound Doppler can be used as a non-invasive tool to assess the renal circulation.[7,8] Renal Resistive Index (RRI) is a sonographic measurement of resistance to flow in intrarenal arcuate or interlobar arteries. An inverse relationship between MAP and RRI has been strongly demonstrated, owing to the post-glomerular vasoconstriction

during hypoperfusion to maintain GFR.[7] It was found that patients in shock have a higher RRI when compared to patients without shock.[9,10]

Recommendations suggest to use second vasopressor to reduce the dose of first vasopressor considering side effects of high dose of norepinephrine.[2] However none of the above vasopressors were proven to be strongly beneficial after Nor-Epinephrine and no definitive strong recommendations were made regarding the second choice of vasopressor.[2]The major objective of this study was using Doppler RRI as a surrogate marker and early index of hypoperfusion and to demonstrate the beneficial effect of dobutamine on organ perfusion. The secondary aim was to assess the relationship of RRI to AKI and lactate in septic shock.

AIMS AND OBJECTIVES

- **Primary objective:**
  1. To evaluate the effect of dobutamine on Renal Resistive Index in septic shock patients.
- **Secondary objective:**
  1. To assess the relationship of RRI with lactate in septic shock.
  2. To assess the relationship of RRI with AKI in septic shock.

REVIEW OF LITERATURE

Sepsis is a life-threatening complication in response to infection causing end-stage organ dysfunction and death. The word sepsis is derived from greek term “σήψις” which means “make rotten” or “decomposition”. The term was first described by Hippocrates in 400 BCE to describe the process through which infected wounds become purulent. Although the term sepsis dated old, it took over more than 2000 years to understand the pathophysiology of sepsis.[11] Despite advancements in the understanding of the clinical syndrome, hemodynamic monitoring devices and treatment modalities, sepsis is still one of the leading causes of mortality in ICU patients.[12]

Globally, more than 30 million people are affected by sepsis every year worldwide, with 6 million deaths occurring annually.[12] It is estimated to affect 1 to 1.5 million persons per year in United States of America (USA) causing more than 200,000 deaths every year.[12] As per SSC 2012 data, mortality rates due to sepsis are 41% in Europe compared to 28.3% in USA.[12]

Definitions:

Sepsis 3 (2016): “Sepsis is a life-threatening organ dysfuction caused by dysregulated host response to infection”.[1,2]

Clinical criteria for sepsis: Suspected or documented infection and an acute increase of ≥2 SOFA points.[12]

The task force considered that positive qSOFA (quick SOFA) criteria should also prompt consideration of possible infection in patients not previously recognized as infected.[11,12]

qSOFA criteria:

Altered mental status (GCS score <15)

Systolic blood pressure <100 mm Hg

Respiratory rate >22 breaths per min

Septic shock is defined as “ subset of sepsis in which underlying circulatory and cellular metabolism abnormalities are profound enough to substantially increase mortality.”[1,2]

Septic shock can be identified with a clinical construct of sepsis with persisting hypotension, requiring vasopressor therapy to elevate MAP ≥65 mm Hg and lactate >2 mmol/L despite adequate fluid resuscitation.[1,2,13]

The paramount importance in the management of patients with sepsis and septic shock is that it is a medical emergency requiring assessment and management on urgent basis. This lead to further modification of the SSC 2016 guidelines with an update in 2018.[1]

HOUR-1 BUNDLE
1. Measure lactate level. Remeasure if initial lactate is >2mmol/L 2. Obtain blood cultures prior to administration of antibiotics 3. Administer broad-spectrum antibiotics 4. Begin rapid administration of 30ml/kg crystalloid for hypotension or lactate ≥4 mmol/L 5. Apply vasopressors if patient is hypotensive during or after fluid resuscitation to maintain MAP ≥65 mm Hg.

These guidelines were further updated in October 2021 by SSC with an emphasis on improving care of sepsis patients after discharge from ICU. Newer guidelines specially address challenges to treat patients experiencing long-term effects of sepsis.[5]

Early effective resuscitation is crucial to prevent organ hypoperfusion in a patient with septic shock. Hence, initial fluid resuscitation with 30ml/kg crystalloids should be initiated immediately upon recognizing patient with sepsis, elevated lactate and/or hypotension (strong recommendation, low quality evidence). Fluid administration beyond initial resuscitation needs careful reassessment

as a sustained positive balance can be detrimental.[1,2,5] This reassessment includes physiological variables such as blood pressure, heart rate, urine output, noninvasive monitoring by PLR, PPI, IVC collapsibility index and invasive monitoring such as SPV, PPV, CVP. In patients not responding to fluids, they are managed by vasoactive agents to maintain a MAP ≥65 mm Hg.[2]

Norepinephrine is the firstchoice vasopressor recommended (strong recommendation, moderate quality evidence).[2,5] Norepinephrine increases MAP due to its vasoconstrictive effects, with little changes in heart rate and more effective at reversing hypotension in patients with septic shock. However, a high dose of norepinephrine can cause organ hypoperfusion, bowel ischemia, increase cellular energy expenditure, hyperglycemia.[14] Hence, SSC guidelines 2021 suggests adding vasopressin (0.03U/min) (weak recommendation, moderate quality evidence) followed by epinephrine (weak recommendation, low quality of evidence) with an intent to decrease the nor-epinephrine dosage.[5]

Dobutamine is suggested in patients with evidence of persistent hypoperfusion despite adequate fluid resuscitation and use of other vasopressor agents (weak recommendation, low quality evidence).[5] The end point of the resuscitation is ultimately determined by the organ perfusion and the vasopressor's dosage should be titrated accordingly.[2,5]

Although vasopressor support reverses hypotension but it does not reflect organ perfusion. Serum lactate is used a surrogate marker of organ perfusion according to SSC guidelines. If the initial lactate is >2mmol/L, it is remeasured within 2-4h to guide resuscitation to normalize lactate (Weak recommendation, low quality evidence).[1] However, serum lactate is not a direct measure of organ perfusion. Serum lactate is increased in sepsis due to various other reasons such as hepatic failure, renal failure, myeloproliferative disease, pancreatitis, short bowel syndrome, hypoxia, anemia, regional ischemia and drugs such as catecholamines, biguanides, methanol, ethanol, ethylene glycol.[6] A single lactate measurement cannot guide in resuscitation and sequential measurements are required to guide treatment. Serum

lactate measurement is an indirect nonspecific indicator of organ hypoperfusion, hence a more sensitive and specific indicators of organ hypoperfusion are needed to guide therapy.[2,6]

Septic shock is a severe condition which organ hypoperfusion. The most common affected organ is kidney. Acute kidney injury is seen in 25% of cases with sepsis and 50% of septic shock patients in ICU.[7] AKI increases morbidity and morbidity in septic shock patients if not addressed early in the course of disease. Underlying mechanism of AKI can be either organ hypoperfusion and/or cellular injury due to oxidative stress or drug toxicity.[9]

Many markers have been recognized to assess early predictors of AKI such as neutrophil gelatinase-associated lipocalin, tissue inhibitor of metalloprotease-2, kidney injury molecule-1 and insulin-like growth factor binding protein-7. However, none of these markers have shown any proven benefit in management of AKI patients. Insteadthey are not found to be cost-effective and are time taking.[15]Routine monitoring of the circulation includes pressure as well as flow measurements in the macro-circulation to guide the administration of fluids and vasoactive medication. However, it does not include the renal circulation. Bedside ultrasound Doppler of renal vessels is a noninvasive, easily accessible, repeatable tool which gives a real time monitoring of renal persfusion.[9,15]The changes in Renal resistive index (RRI) are noted earlier before the changes in serum creatinine during both development and recovery phase of AKI.[15]

RRI has good sensitivity and specificity in diagnosing AKI, even in patients on vasoactive agents. A RI >0.795 predicted AKI with 82% sensitivity and 92% specificity.[15] Renal Resistive Index (RRI) is a sonographic measurement of resistance to flow in intrarenal arcuate or interlobar arteries. Renal Resistive Index is calculated as (Vmax – Vmin)/ Vmax, where Vmax = peak systolic velocity and Vmin = minimal diastolic velocity.[15]High RRI can be caused by vasoconstriction, decreased vascular compliance, or capillary rarefaction, and is associated with renal arterial disease.[4] RRI seems a promising tool to predict the development and reversibility of AKI in critically ill patients

Rozemeijer et al., in his prospective observational study on renal resistive index in shock. They analyzed 40 patients with shock and 52 without shock. Among 40 patients with shock, 29 (72.5%) had cardiogenic shock, 3 (7.5%) had hypovolemic shock, 6 (15.0%) had septic shock, and 2 (5.0%) had shock due to SIRS. Patients with shock had a significantly higher RRI than patients without shock (0.751 [0.692–0.788] vs. 0.654 [0.610–0.686], respectively, P<0.001) RRI was not significantly different between patients with septic shock (n=6) and other shocks (n=34): 0.760 [0.647–0.789] vs. 0.751 [0.694–0.789] respectively, P=0.956.This study concluded that patients with shock had a higher RRI than patients without shock.[10]

Deruddre et al., condsucted a study on effect of MAP on renal resistive index in septic shock. It was prospective, single-center, nonrandomized, open-label trial in the surgical intensive care unit including 11 patients with septic shock who required fluid resuscitation and norepinephrine to increase and maintain MAP at or above 65 mmHg. Norepinephrine was titrated during three consecutive and not randomized periods of 2 h to achieve a MAP at successively 65, 75, and 85 mmHg. At the end of each period hemodynamic parameters and renal function variables (urinary output, creatinine, clearance) were measured, and Doppler ultrasonography was performed on interlobar arteries to assess the renal resistive index. When increasing MAP from 65 to 75 mmHg, urinary output increased significantly from 76 +/- 64 to 93 +/- 68 ml/h and the resistive index significantly decreased from 0.75 +/- 0.07 to 0.71 +/- 0.06. No difference was found between 75 and 85 mmHg. Thus, they concluded that Doppler ultrasonography and RRI measurementshelps to determine the optimal MAP needed for renal blood flow to be maintained and to titrate the hemodynamic resuscitation in septic shock.[17]

You fu et al., in his prospective observational study to explored combined value of renal resistive index and central venous pressure to predict AKI in septic shock A total of 107 patients were enrolled, with 59 patients in AKI group and 48 patients in non-AKI group. Logistic regression analysis showed that high CVP (OR= 1.2), RRI (OR: 3.02),

lactate (OR= 2.43) and PCT (OR= 1.20) were independent risk factors for septic shock induced AKI. This study concluded that high CVP and RRI were independent risk factors for septic shock induced AKI. [18]

Jianing Zhu et al., in a systematic review and meta-analysis of cohort studies assessed the efficacy of RRI in predicting AKI in critically ill patients. Prospective studies that examined the diagnostic accuracy of RRI in AKI were included. Among the 126articles identified, 18 were included, with a total of 1656 patients. Bivariate analysis yielded pooled sensitivity and specificity of 0.81 (95% CI 0.74-0.86) and 0.75 (95% CI 0.65-0.83), respectively. The summary positive likelihood ratio was 3.2 (95% CI 2.2-4.6), and negative likelihood ratio was 0.26 (95% CI 0.19-0.36). They concluded that elevated RRI may be an early predictor of AKI in critically ill patients and further large-scale prospective studies are needed to confirm the predictive efficacy and determine the performance and optimal cutoff value of RRI.[19]

Antal et al., studied the association between the macrohemodynamic profile and sepsis induced acute kidney injury (AKI) and investigated minimally invasive hemodynamic parameters to identify patients at risk for sepsis-AKI. They included 71 patients with sepsis and septic shock after initial fluid resuscitation using local protocols and continued to give fluids guided by the minimally invasive hemodynamic parameters. They assessed the hemodynamic status by transpulmonary thermodilution technique. Sequential organ failure assessment (SOFA score) (AUC 0.74, 95% CI 0.61–0.83, $p < 0.01$) and cardiovascular SOFA (AUC 0.73, 95% CI 0.61–0.83, $p < 0.01$) were found to be predictors for sepsis-induced AKI, with cut-off values of 9 and 3 points respectively. Persistent low stroke volume index (SVI) ≤ 32 mL/m2/beat (AUC 0.67, 95% CI 0.54–0.78, $p < 0.05$) and global end-diastolic index (GEDI) < 583 mL/m2 (AUC 0.67, 95% CI 0.54–0.78, $p < 0.05$) after the initial fluid resuscitation were predictive for oliguria/anuria at 24 h after study inclusion. The combination of higher vasopressor dependency index and norepinephrine, lower systemic vascular resistance index (SVRI), and mean arterial blood pressure (MAP) levels, in the setting of normal preload parameters, showed a more severe vasoplegia. They

concluded that severe vasoplegia in first 24hours as determined by low SVR through the need of vasopressors to maintain a MAP ≥65 mm Hg in absence of hypovolemia was associated with higher risk of sepsis induced AKI.[17] Also, SOFA and cardiovascular SOFA scores may identify patients at risk for sepsis AKI.[20]

In septic shock, nor-epinephrine is the first choice of vasopressor according to SSC guidelines (strong recommendation, moderate quality evidence).[2]However, no strong recommendations have been made regarding the second choice of vasopressor after nor-epinephrine.[2] The patient outcome with the use of specific vasopressor is unpredictable. Hence, the question of ideal ionotrope/vasopressor in patients with septic shock remains unanswered and controversial.[21]

Kasugai et al., performed retrospective single-center observational study using data from adult patients (≥ 18 years old) admitted to emergency and medical intensive care unit (ICU) who had received epinephrine to treat norepinephrine-refractory septic shock. The response was considered positive if there was increase in mean arterial pressure of 10 mmHg or decrease in arterial lactate level 3 h after epinephrine administration. Forty-one patients were included: 24 responders (59%) and 17 non-responders (41%). Responders showed higher rate of survival from shock ($P < 0.001$), and 28-day survival ($P < 0.001$). In multivariable analysis, time of epinephrine administration after ICU admission ($P = 0.011$) and SOFA score (p= 0.034) were associated with epinephrine response. Time of epinephrine administration was also significantly associated with survival from shock ($P = 0.005$) and 28-day survival ($P = 0.006$), while SOFA score did not. Epinephrine administration later than 24 h after ICU admission was associated with poor response (; $P < 0.001$).A better hemodynamic status in refractory shock patients was observed with early administration of epinephrine in norepinephrine refractory shock.[23]

Mahmoud et al., compared the effect of dobutamine and epinephrine to norepinephrine in treating septic shockpatients

refractory to fluid therapy. Dobutamine versus epinephrine to norepinephrine in treating septic shock patients refractory to fluid therapy. Upon reaching the dose of 0.1 µg/kg/min, patients with mean arterial pressure <70 mmHg were further divided randomly into two equal groups. In group I, the patients were continued on norepinephrine and dobutamine was added at a starting dose of 3 µg/kg/min and increased in increments of 2 µg/kg/min up to 20 µg/kg/min. In group II, the patients were continued on norepinephrine and epinephrine was added in a starting dose of 0.05 µg/kg/ min and increased in increments of 0.03 µg/kg/min up to 0.3 µg/kg/min. They addition of epinephrine to norepinephrine had positive effects on the cardiovascular parameters but negative results on the serum lactate concentration and systemic pH compared with the addition of dobutamine to norepinephrine. [21]

DijillaliAnnane et al., conducted aprospective, multicentre, randomized, double-blind study in 330 patients with septic shock admitted to one of 19 participating intensive care units in France. Patients were assigned to receive epinephrine (n=161) or norepinephrine plus dobutamine (n=169), which were titrated to maintain mean blood pressure at 70 mm Hg or more. At day 28, there were 64 (40%) deaths in the epinephrine group and 58 (34%) deaths in the norepinephrine plus dobutamine group (p=0.31; relative risk 0.86, 95% CI 0.65-1.14). There was no significant difference between the two groups in mortality rates at discharge from intensive care(p=0.69), at hospital discharge (p=0.51), and by day 90 (p=0.73), time to haemodynamic success (p=0.67), time to vasopressor withdrawal (p=0.09), and time course of SOFA score. Rates of serious adverse events were also similar. Hence, they concluded that there was no difference in safety and efficacy between epinephrine alone and norepinephrine plus dobutamine for the management of septic shock.Nadeem et al, conducted meta-analysis on effect of dobutamine in septic shock patients. A total 11 studies with 21 data sets including 239 patients were pooled for meta-regression analysis. This analysis was performed for VO_2, DO_2, CI, and O_2 extraction. Age was found to

be significant confounding factor for cardiac index (CI), delivery of oxygen (DO_2), and O_2 extraction. APACHE score was not found to be a significant confounding factor for any of the parameters. Dobutamine seems to have a positive effect on cardiovascular parameters in patients with septic shock and found that cardiovascular parameters in the form of VO2, CI, DO2, RAP and O2 extraction improved with dobutamine in septic shock patients with no significant changes in HR, MAP,PaO_2.[24]

Carolina Enrico et al., in his study on microcirculatory and systemic effects of dobutamine in septic shock patients. Systemic hemodynamics and sublingual microcirculation were evaluated with dobutamine at different doses (0, 2.5, 5.0, and 10.0 μgkg(-1) min(-1)) in 23 patients with septic shock. Dobutamine increased heart rate, cardiac index, and stroke volume index (SVI). Mean blood pressure was unchanged, and systemic vascular resistance decreased. Individual responses were heterogeneous. Stroke volume index increased in 52% of the patients. These patients showed lower changes in mean blood pressure ($P < .05$) and higher increases in cardiac index than did non-responders. Changes in SVI significantly correlated with echocardiographic left ventricular ejection fraction ($r = 0.55$). In the whole group, perfused capillary density remained unchanged but improved if basal values were 12 mm/mm(2) or less. They concluded that dobutamine produced variable hemodynamic effects and stroke volume index was increased only in patients with cardiac systolic dysfunction on echocardiography. Improvement in sublingual microcirculation was observed when they were severely altered at baseline.[25]

Andre F Gosling et al., studied the renal-resistive index for prediction of acute kidney injury. As reliance on serum creatinine accumulation to confidently diagnose it leads to a significant and important delay (up to 48 hours). Hence, a search for earlier AKI biomarkers is warranted. The renal-resistive index (RRI) was a promising early AKI biomarker that reflects intrarenal arterial pulsatility as reflected by the peak

systolic and end-diastolic blood velocities divided by the peak systolic velocity. [26]

The effect of ionotropic support on hemodynamic parameters and organ perfusion needs to be established, as there were not many studies on it. Owing to this lacunae, present study focused on the role of dobutamine in patients with septic shock with organ hypoperfusion measured by RRI despite maintained MAP following nor-epinephrine support. This present study focuses on dobutamine in septic shock patients using renal resistive index as a monitoring tool to titrate the hemodynamic resuscitation and evaluate the organ perfusion.

MATERIALS AND METHODS

SOURCE OF DATA

Study design: Prospective observational study

Study place: Intensive care units, Dayanand Medical College, Ludhiana

Study Period: March 2020 to November 2021

METHOD OF COLLECTION OF DATA

Inclusion criteria:

1. All patients admitted to ICU under Critical Care Medicine with septic shock.

Exclusion criteria:

1. Age less than 18 years or older than 75 years.
2. AKI on renal replacement therapy (RRT) or with an expectation of RRT within 24 hours.
3. Known case of renal artery stenosis, chronic kidney disease defined by a glomerular filtration rate of less than 30mL/min/1.73m2.
4. Cirrhosis with hepatorenal syndrome
5. Use of renin-angiotensin-aldosterone antagonists
6. Pregnancy

Definitions:

The Third International Consensus Definitions of Sepsis and Septic Shock (Sepsis-3)[1,2,11]

Sepsis: “Life threatening organ dysfunction caused by a dysregulated host response to infection.” For the sake of clinical operationalization, organ dysfunction is represented by increase in SOFA score of ≥2 points, which is associated with an in-hospital mortality >10%.[1,2,12]

Clinically, any suspected case of infection with an increase in SOFA score of ≥2 points or at least 2 of the following signs:[1,2,12]

qSOFA: Respiratory rate ≥22/min

Altered mental status

Systolic blood pressure <100 mm Hg.

Septic shock: “Sepsis with circulatory and cellular/metabolic dysfunction”, clinically described by a vasopressor requirement to

maintain a MAP ≥65 mm Hg and serum lactate > 2mmol/L in the absence of hypovolemia.[1,2,12]

KIDGO AKI classification:[7]

Stage	Serum creatinine	Urine output
1	1.5-1.9 times baseline Or ≥0.3 mg/dl (26.5µmol/L) increase	<0.5ml/kg/h for 6-12 hours
2	2.0- 2.9 times baseline	<0.5ml/kg/h for ≥12h
3	3.0 times baseline OR Increase in serum creatinine to ≥ 4.0 mg/dl (≥353.6 µmol/L) OR Initiation of renal replacement therapy OR, In patients <18 years, decrease in eGFR to <35ml/min per 1.73 m^2	<0.3 ml/kg/h for OR ≥ 12 hours Or Anuria for ≥ 12hours

Study Protocol: All patients of septic shock in ICU included in the study were resuscitated according to SSC guidelines. Patients with septic shock were initially resuscitated with crystalloids to maintain a MAP ≥65 mm Hg. The adequacy of fluid resuscitation was monitored by CVP (8-12 mm Hg), PPV (<13%) and PLR test.[1,2] Following adequate resuscitation, if the MAP still remained less than 65 mm Hg then nor- epinephrine was used as the first line vasopressor.[2]Nor-epinephrine infusion was started at a dose of 0.05µg/kg/min and gradually increased to 0.2µg/kg/min. Once the mean arterial pressure (MAP) was>65 mm Hg, dobutamine was started at a dose of 3µg/kg/min if organ hypoperfusion was present. Organ hypoperfusion was measured on the basis of lactate (>2mmol/dl) along with decreased urine output or reduced ejection fraction on

echocardiography. In case if MAP falls below 65 mm Hg despite the above ionotropic support, vasopressin was added as a rescue drug in a dose upto 0.03U/min.

The response to vasopressors/ionotropes and resuscitation was monitored by vital parameters such as heart rate, MAP and urine output. Patient vital parameters, dose of ionotropes, serum lactate, CVP, IVC diameter, PPV and RRI were monitored at admission, 1-hr, 6-hrs, 12-hrs, 24-hr and 48-hrs following start of ionotropes. S.Creatinine was measured every day for 72 hours. SOFA score was measured everyday for 72 hours.

Renal Resistive Index measurements:

Bedside Doppler ultrasonography was performed with a 7.5 MHz transducer, using a previously described RI measurements technique. Using sonography one of the kidneys was identified and interlobar arteries localized using colour Doppler mode. Pulse-wave Doppler was used to measure blood velocities in the inter-lobar arteries. Peak systolic and end-diastolic velocities were measured in 3 consecutive pulses. Resistive Index was calculated as: RI= (peak systolic velocity – end-diastolic velocity)/peak systolicvelocity.[27,28] The RI values presented were an average of the 3 measures performed on the 3 consecutive pulses. Normal values are reported between 0.48 and 0.7.[29]

Parameters collected at each RRI measurement:

On each RRI measurement, following data were recorded: HR, systolic, diastolic and mean arterial pressures, vasopressors doses, lactate, IVC diameter, PPV, CVP and urine output.

Other data: The following data was recorded:

Age, admission weight, past medical history of any comorbidities, general and systemic examination, hemogram, RFT, s.electrolytes, LFT, Chest X-ray and SOFA score.

Statistical Analysis:

Sample size:

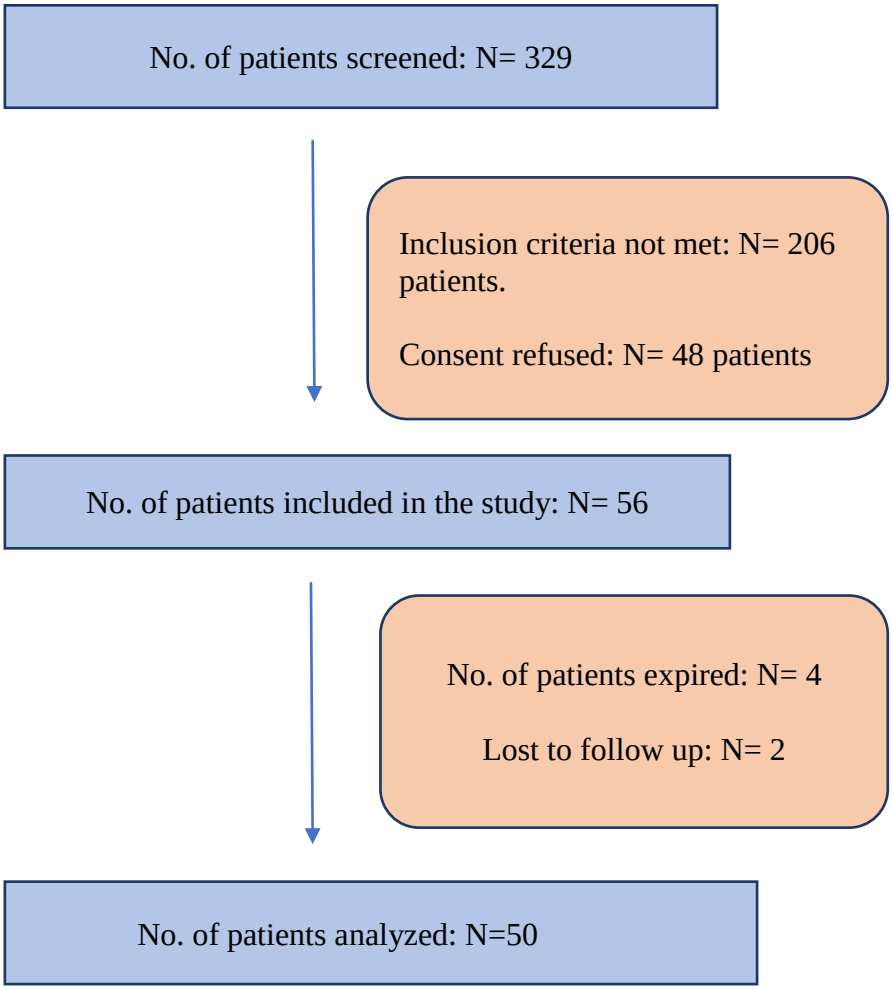
A mean sample size: 50 patients.

Data were described in terms of range; mean ±standard deviation (± SD), median, frequencies (number of cases) and relative frequencies (percentages) as appropriate. Comparison of quantitative variables between the study groups was done using Student t-test and Mann Whitney *U* test for independent samples for parametric and non-parametric data respectively. For comparing categorical data, Chi square ($\chi 2$) test was performed and exact test was used when the expected frequency is less than 5. A probability value (*p* value) less than 0.05 was considered statistically significant. All statistical calculations were done using SPSS (Statistical Package for the Social Science) SPSS 21 version statistical program for Microsoft Windows.

OBSERVATIONS AND RESULTS

A total number of 329 septic shock patients admitted to intensive care units of the hospital were screened for eligibility. Out of 329 septic shock patients screened, 206 patients did not meet inclusion criteria, 48 patients refused consent, 19 patients required RRT during the study period and so excluded from the study. While 4 patients expired during the study period and 2 patients could not be followed for 28 days. Hence 50 patients were analyzed during the 12 months study period (capture rate: 15.2%).

Figure 1: Trial profile


No. of patients screened: N= 329
Inclusion criteria not met: N= 206 patients.
Consent refused: N= 48 patients
No. of patients included in the study: N= 56
No. of patients expired: N= 4
Lost to follow up: N= 2
No. of patients analyzed: N=50

Data depicted as N= number

Demographic data and patient characteristics:

The demographic data of the patients is shown in table 1 and figures 2 3 ,4 & 5, 6, 7 & 8. The mean age of the patients included in the study is 48.16 ± 15.04. There were 32 (64%) males and 18 (36%) females in the study population. The mean height of the population was 166. ±6.66cms and the mean weight was 72.4±6.88 kgs. Majority of the patients were post-operative following a major surgery 31 (62%) and the rest of them following medical conditions n=19 (38%). The primary source of infection in most of the patients was abdomen n=23 (46%), followed by lung 9 (18%), soft tissue infection, primary septicemia and central nervous system. The most commonly isolated micro-organism is a gram-negative bacteria n=36 (76%), followed by anaerobes n= 12 (24%), followed by gram positive bacteria, fungi and viruses.

Table 1: Demographic profile and characteristics of the study:

Parameters	Number of patients (%)
Age (years)	48.16±15.04
Height (cm)	166.5±6.66
Weight (kg)	72.4±6.88
Sex: Males Females	 32 (64%) 18 (36%)
Type of patient: Medical Surgical	 19 (38%) 31 (62%)
Primary source of infection: Lung Abdomen Urinary tract Soft tissue/ joints/ bones Primary septicemia Central nervous system	 9 (18%) 23 (46%) 3 (6%) 8 (16%) 6 (12%) 1 (2%)
Micro-organism: Gram positive bacteria Gram negative bacteria Anaerobes Mycobacteria Fungi Virus	 6 (12%) 38 (76%) 12 (24%) 2 (4%) 7 (14%) 1 (2%)

Data depicted as N= number, % = percentage, cm = centimeter, Kg = Kilogram

Figure 2: Box plot showing age of patients in years

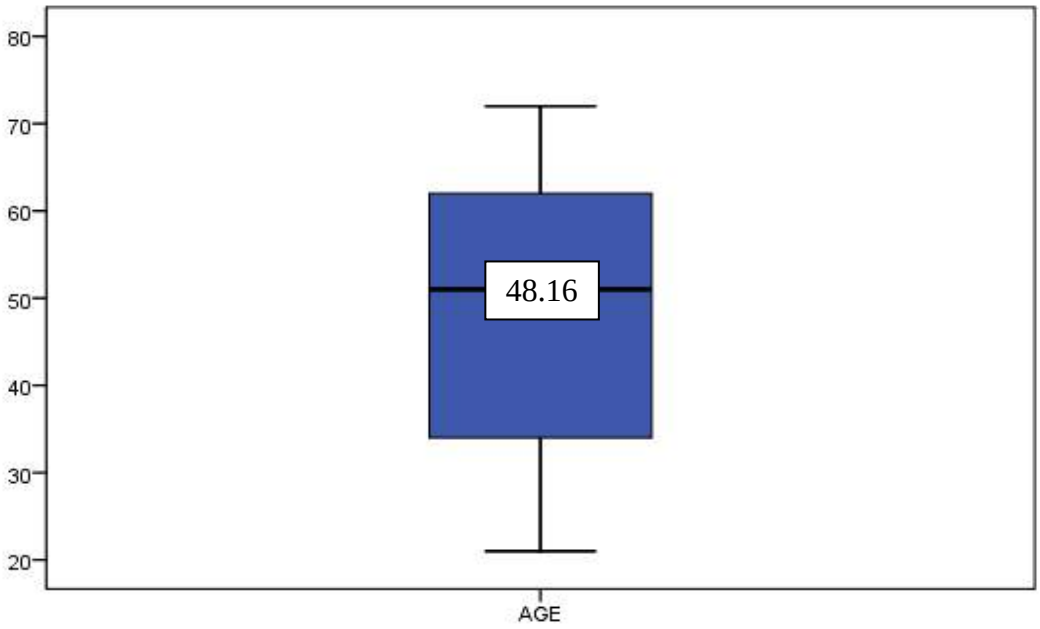
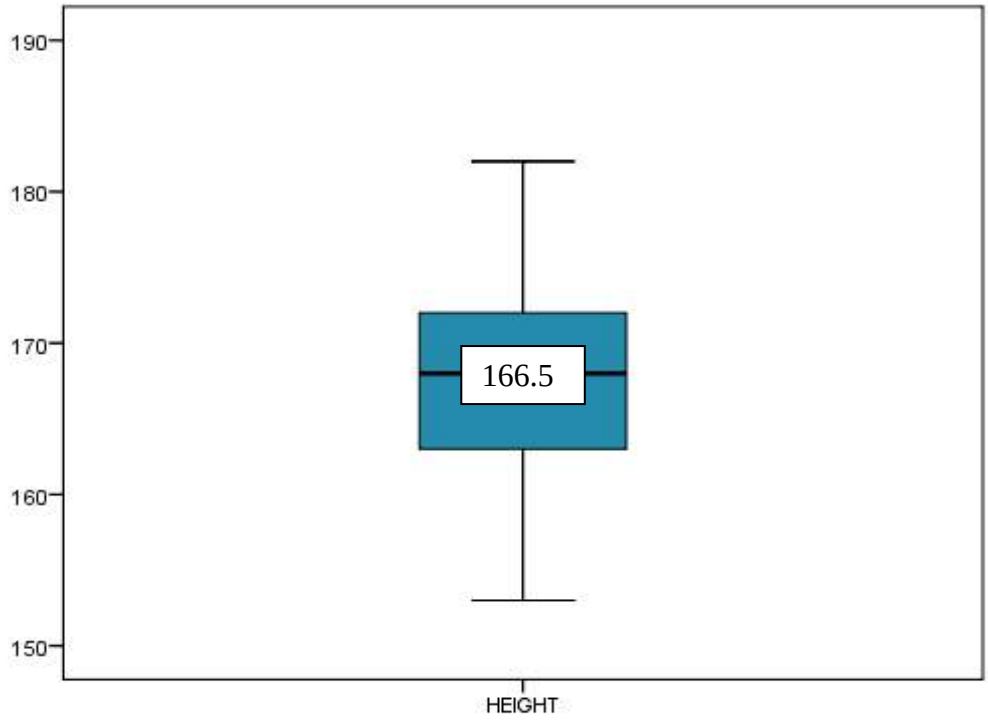
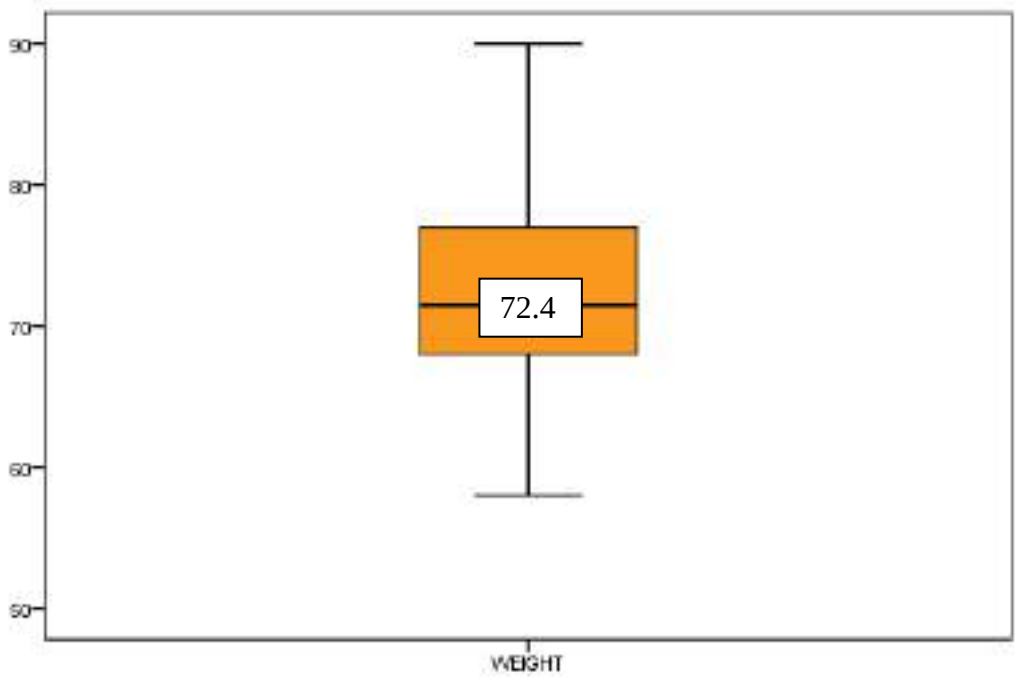


Figure 3. Box plot- showing height of patients in cm



Cm = centimeters

Figure 4. Box plot- showing weight of patients in kg



Kg- kilogram

Figure 5. Gender distribution of the study population

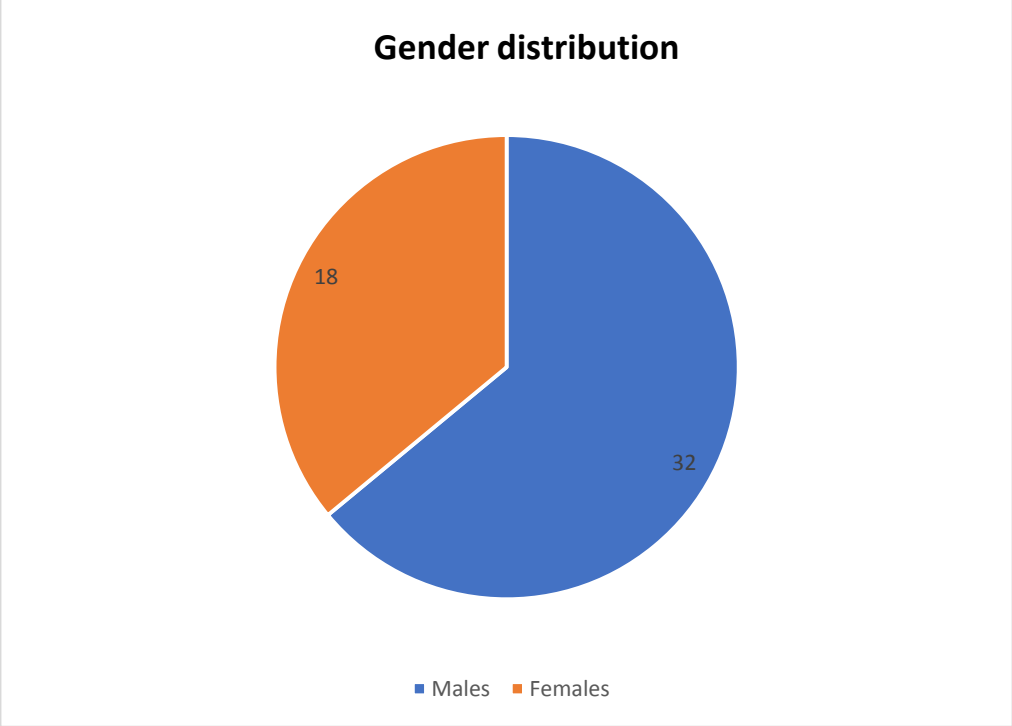


Figure 6. Type of patient of the study population

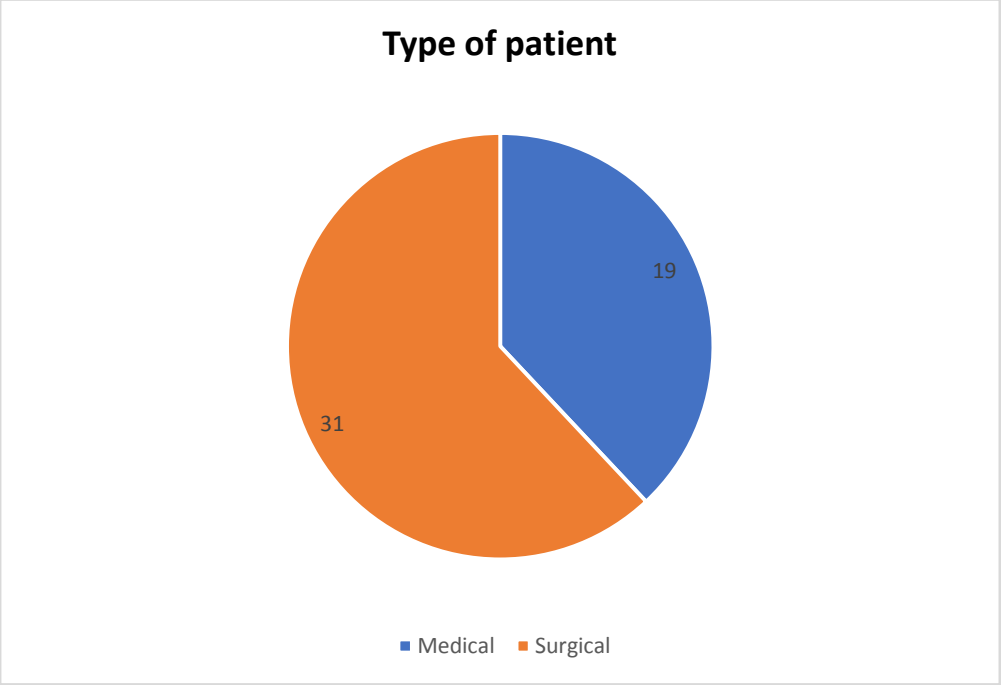


Figure 7. Source of Infection of the study population

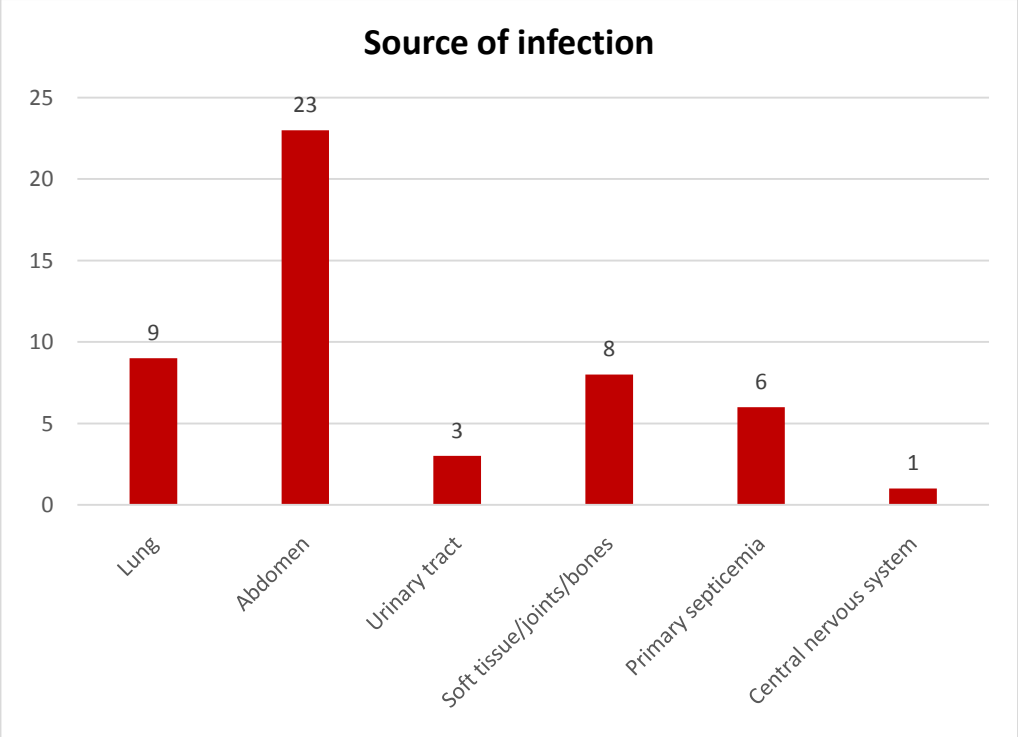
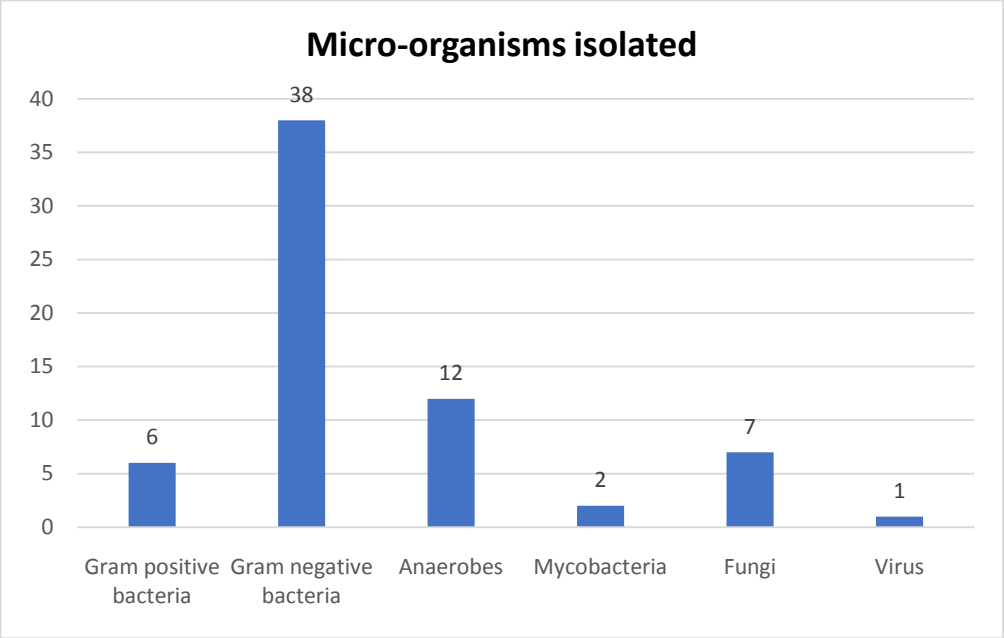


Figure 8. Micro-organisms isolated from the patients of study population



General characteristics of the patients:

General characteristics of patient depicted in Table 2 and figure 9.

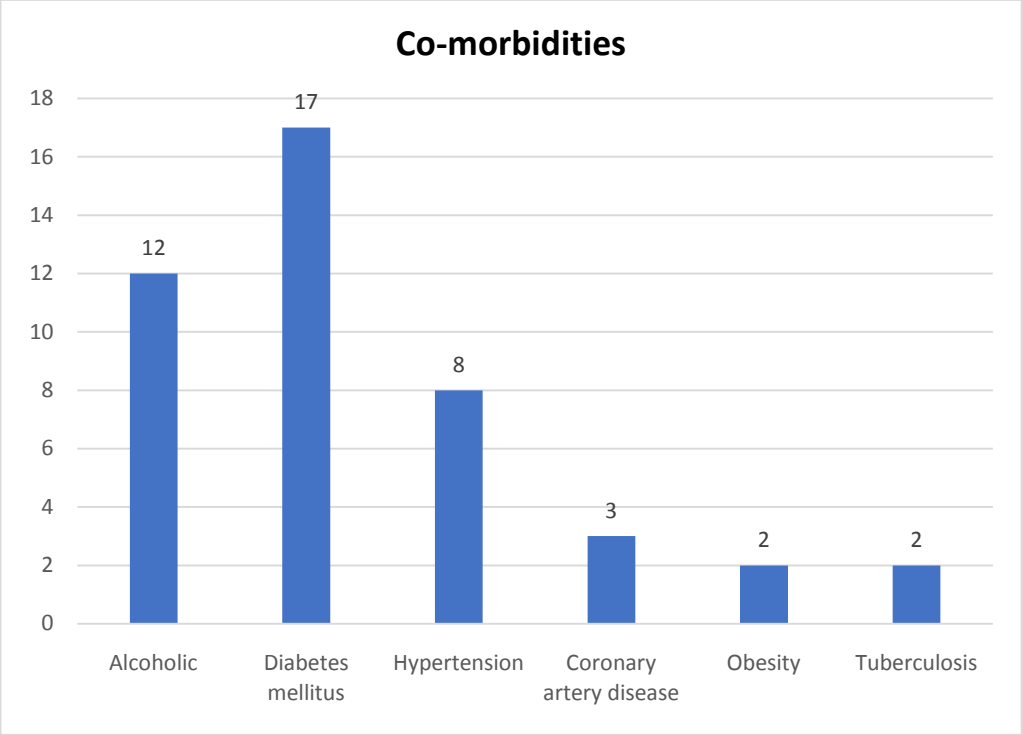
The most common co-morbid condition associated was Diabetes mellitusaffecting17 (34%), followed by alcohol consumption in 12 (24%), hypertension in 8 (16%), coronary artery disease in 3 (6%), obesity in 2 (4%) and tuberculosis in 2 (4%) patients. The mean SOFA score on ICU admission was 9.76 ± 2.24. The mean hematocrit of the patients was 11.34% ± 2.08. A total of n= 38 (76%) patients received mechanical ventilation and acute kidney injury was seen in n= 34 (68%) patients.

Table 2: General characteristics of the patients

Parameters	Number/ Mean
SOFA score on ICU admission	9.76 ± 2.24
Co-morbid conditions Alcoholic Diabetes Mellitus Hypertension Coronary artery disease Obesity Tuberculosis	 12 (24%) 17 (34%) 8 (16%) 3 (6%) 2 (4%) 2 (4%)
Hematocrit (%)	11.34±2.08
No. of patients receiving mechanical ventilation	38 (76%)
No. of patients with acute kidney injury	34 (68%)

% = percentage

Figure 9. Co-morbid conditions associated with study population



Initial resuscitation of the patients:

There was a statistically significant improvement in vital parameters, PPV, CVP, IVC diameter, RRI and serum lactate levels.

Table 3: Parameters before and after fluid resuscitation

Parameter	Before resuscitation	After resuscitation	p- value
Heart Rate (/min)	145.64	130.04	0.001
Mean arterial pressure (mm Hg)	61.12	71.12	0.001
CVP (cm H2O)	4.86	9.78	0.001
PPV (%)	15.58	9.62	0.001
IVC diameter (cm)	1.13	1.51	0.001
s.Lactate (mmol/dl)	7.13	5.85	0.001
RRI	0.75	0.72	0.001
Urine output (ml/hr)	10.8	21.4	0.001

/min= per minute, %= percentage, ml/hr= milliliter per hour

Dose of Nor-epinephrine at different time points after the start of ionotropic support:

There was a statistically significant increase (p= 0.001) in the dose of Nor-epinephrine at the start of dobutamine support. Later the Nor-epinephrine dose decreased at 6 hours and 12 hours which was not statistically significant (p value > 0.05). There was a statistically significant decrease in the dose of Nor-epinephrine at 24 hours (p= 0.002) and 48 hours(p= 0.001).

Table 4. Dose of Nor-epinephrine at different time points of the study

Dose of Nor-epinephrine (µg/kg/min)	Mean	Std. Deviation	p-value	Mean Difference	Std. Error	95% Confidence Interval for Difference	
						Lower Bound	Upper Bound
Start of Nor-epinephrine	0.21	0.06					
Start of dobutamine	0.24	0.07	0.001	-0.03	0.01	-0.04	-0.01
6Hours	0.23	0.07	0.159	-0.01	0.01	-0.03	0.00
12Hours	0.21	0.08	0.410	0.01	0.01	-0.01	0.03
24Hours	0.19	0.07	0.002	0.03	0.01	0.01	0.05
48Hours	0.17	0.08	0.001	0.05	0.01	0.02	0.08

Dose of dobutamine at different time points after the start of ionotropic support:

Dobutamine infusion was started after MAP >65 mm Hg was achieved following Nor-epinephrine infusion. Dose of dobutamine at different time points depicted in Table 5.

Table 5. Dose of dobutamine at different time points of the study

Dose of dobutamine (µg/kg/min)	N	Minimum	Maximum	Mean	Std. Deviation
Start of dobutamine	50	2.00	5.00	2.74	0.66
6Hours	50	2.00	3.00	2.36	0.48
12Hours	50	1.00	3.00	2.20	0.49
24Hours	50	1.00	3.00	2.14	0.40
48Hours	50	1.00	3.00	1.98	0.51

Dose of vasopressin at different time points after the start of ionotropic support:

Table 6. Dose of vasopressin at different time points of the study

Vasopressin infusion was started when MAP <65 mm Hg after starting dobutamine infusion. Dose of vasopressin at different time points depicted in Table 6

Dose of vasopressin (u/min)	N	Minimum	Maximum	Mean	Std. Deviation
Start of dobutamine	7	0.02	0.04	0.03	0.01
6 Hours	9	0.02	0.04	0.03	0.01
12 Hours	9	0.01	0.02	0.02	0.00
24 Hours	2	0.01	0.01	0.01	0.00

Figure 10. Dose of Nor-epinephrine at different time points

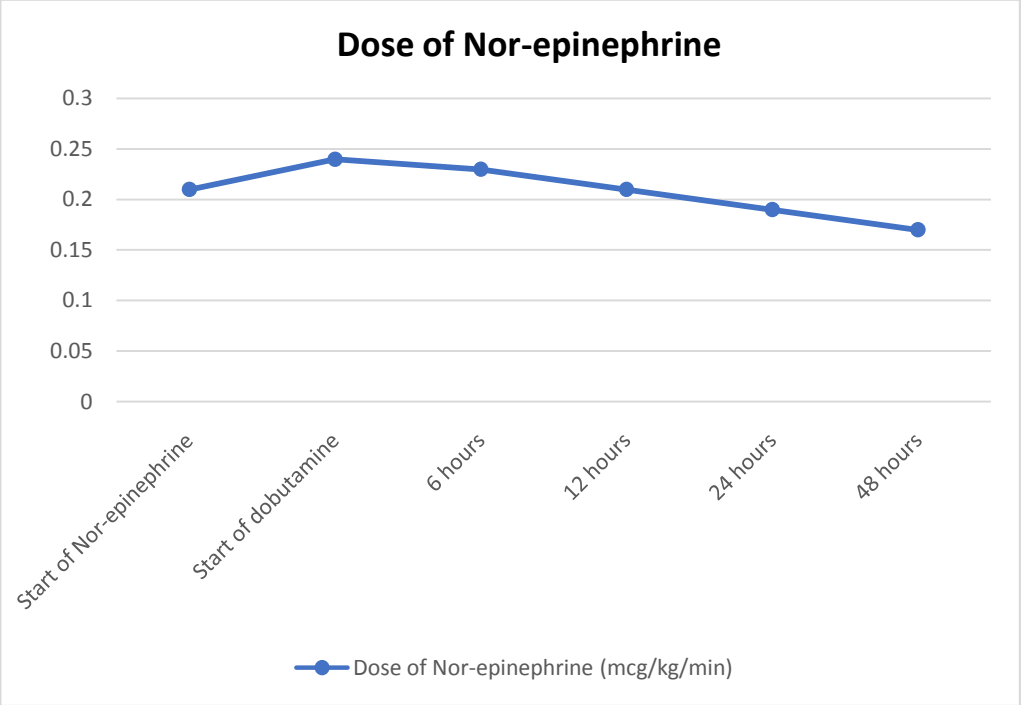


Figure 11. Dose of Dobutamine at different time points

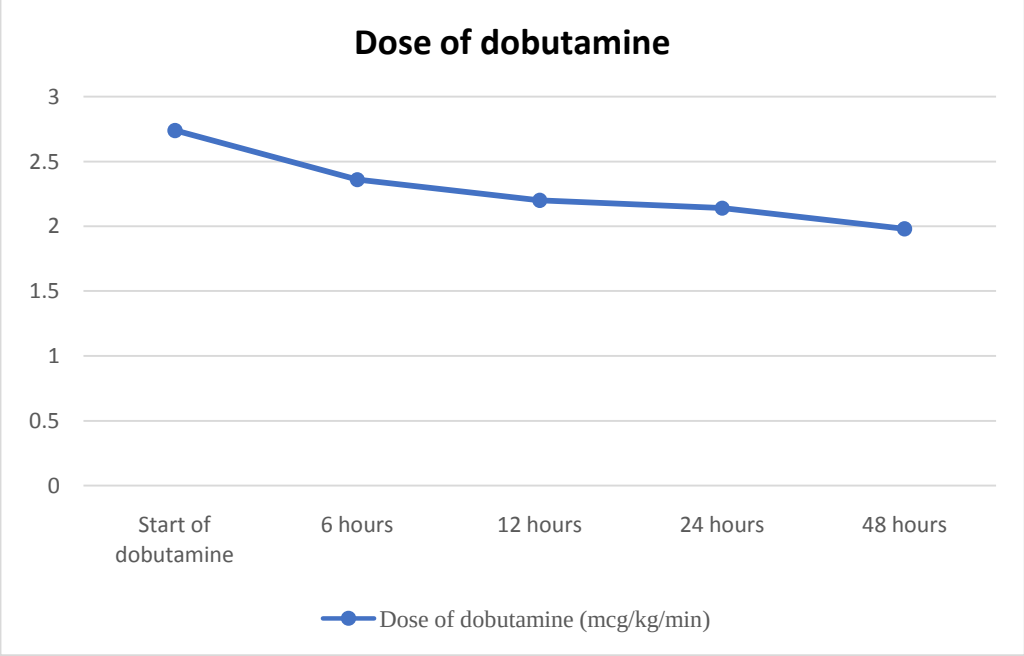
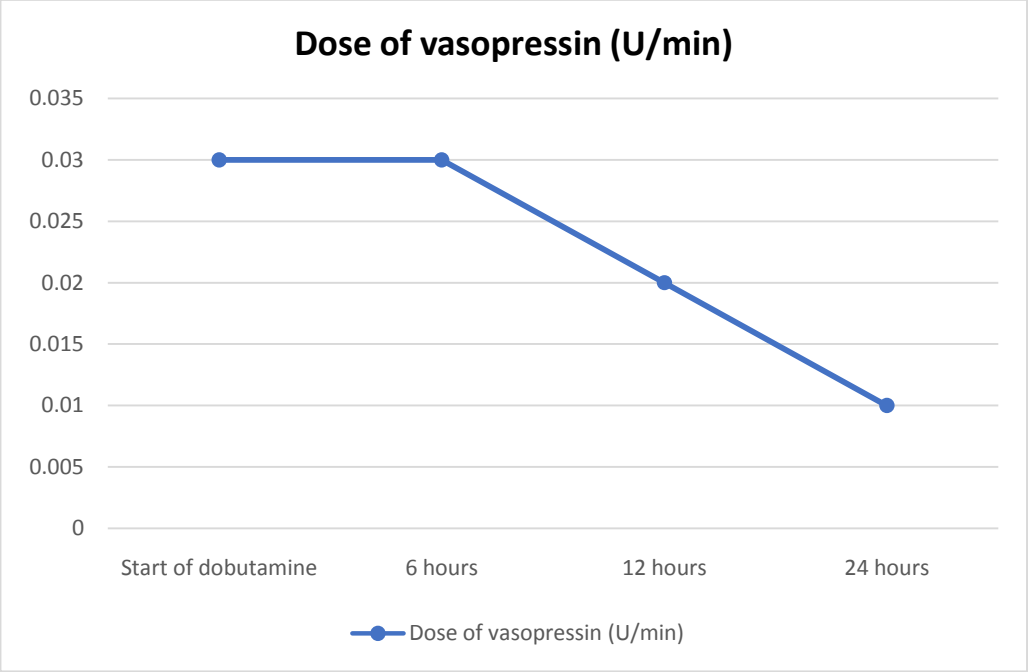


Figure 12. Dose of Vasopressin at different time points



Trends of vital parameters after the start of ionotropic support:

The mean heart rate prior to resuscitation was 145.64±12.22 per minute. The mean heart rate decreased significantly (p= 0.001) following the start of dobutamine and at 6, 12, 24 and 48 hours. The mean arterial pressure also significantly (p= 0.001) increased following the start of dobutamine and at 6, 12, 24 and 48 hours.

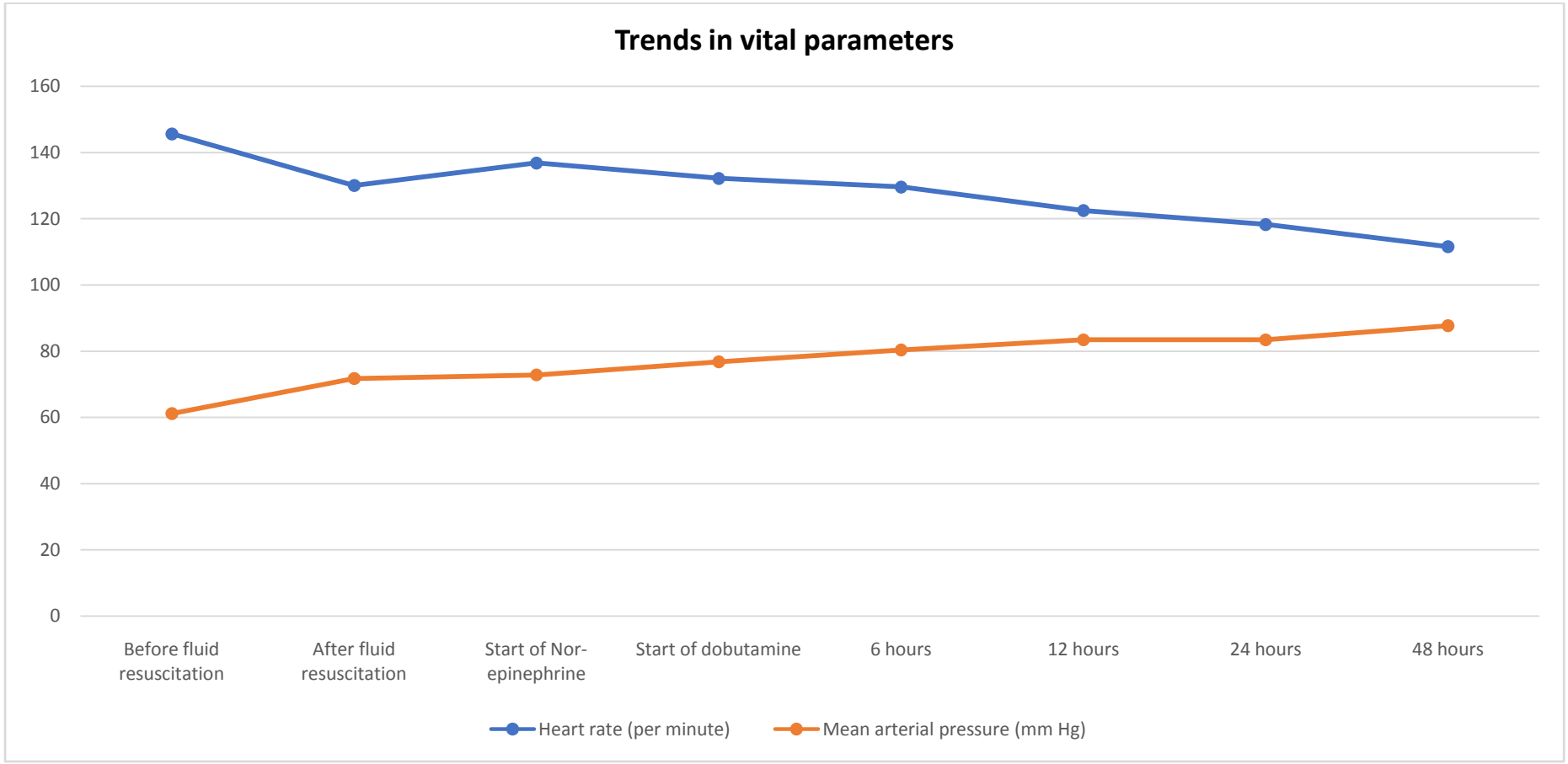
Table 7. Trends of Heart Rate at different time points of the study

Heart Rate (per minute)	Mean	Std. Deviation	p-value	Mean Difference	Std. Error	95% Confidence Interval for Difference	
						Lower Bound	Upper Bound
Before Resuscitation	145.64	12.22					
After Resuscitation	130.04	13.93					
Start of Nor-epinephrine	136.84	11.03					
Start of dobutamine	132.20	9.51	0.001	4.64	1.23	2.17	7.11
6Hours	129.58	11.98	0.001	7.26	1.52	4.21	10.31
12Hours	122.46	10.81	0.001	14.38	1.66	11.05	17.71
24Hours	118.26	9.65	0.001	18.58	1.40	15.77	21.39
48Hours	111.54	9.74	0.001	25.30	1.67	21.94	28.66

Table 8. Trends of Mean arterial pressure at different time points of the study

Mean arterial pressure (mm Hg)	Mean	Std. Deviation	p-value	Mean Difference	Std. Error	95% Confidence Interval for Difference	
						Lower Bound	Upper Bound
Before resuscitation	61.12	4.81					
After resuscitation	71.74	7.06					
Start of nor-epinephrine	72.82	6.895					
Start of dobutamine	76.76	8.847	0.001	-3.94	1.02	-6.00	-1.88
6 Hours	80.38	5.229	0.001	-7.56	1.07	-9.72	-5.40
12Hours	83.44	5.433	0.001	-10.62	0.96	-12.55	-8.69
24Hours	83.44	4.807	0.001	-10.62	1.02	-12.68	-8.56
48Hours	87.72	6.247	0.001	-14.90	1.20	-17.31	-12.49

Figure 13. Trends of vital parameters at different time points of the study



Trends of CVP, PPV and IVC diameter to monitor the fluid status of the patients:

There was no statistically significant difference (p value >0.05) in PPV and IVC diameter at all time points following the initial fluid resuscitation. Although there was no statistically significant difference (p value >0.05) in CVP following the start of dobutamine and 6 hours, there was statistically significant difference (p= 0.001) at 12, 24 and 48 hours.

Table 9. Trends of CVP at different time points of the study

Central Venous Pressure (cm H2O)	Mean	Std. Deviation	p-value	Mean Difference	Std. Error	95% Confidence Interval for Difference	
						Lower Bound	Upper Bound
Before resuscitation	4.86	2.27					
After resuscitation	9.78	1.45					
Start of Nor-epinephrine	11.34	3.17					
Start of dobutamine	11.38	2.42	0.888	-0.04	0.28	-0.61	0.53
6Hours	10.90	2.49	0.270	0.44	0.39	-0.35	1.23
12Hours	10.20	1.95	0.001	1.14	0.41	0.32	1.96
24Hours	9.32	1.60	0.001	2.02	0.38	1.25	2.79
48Hours	9.40	1.50	0.001	1.94	0.49	0.95	2.93

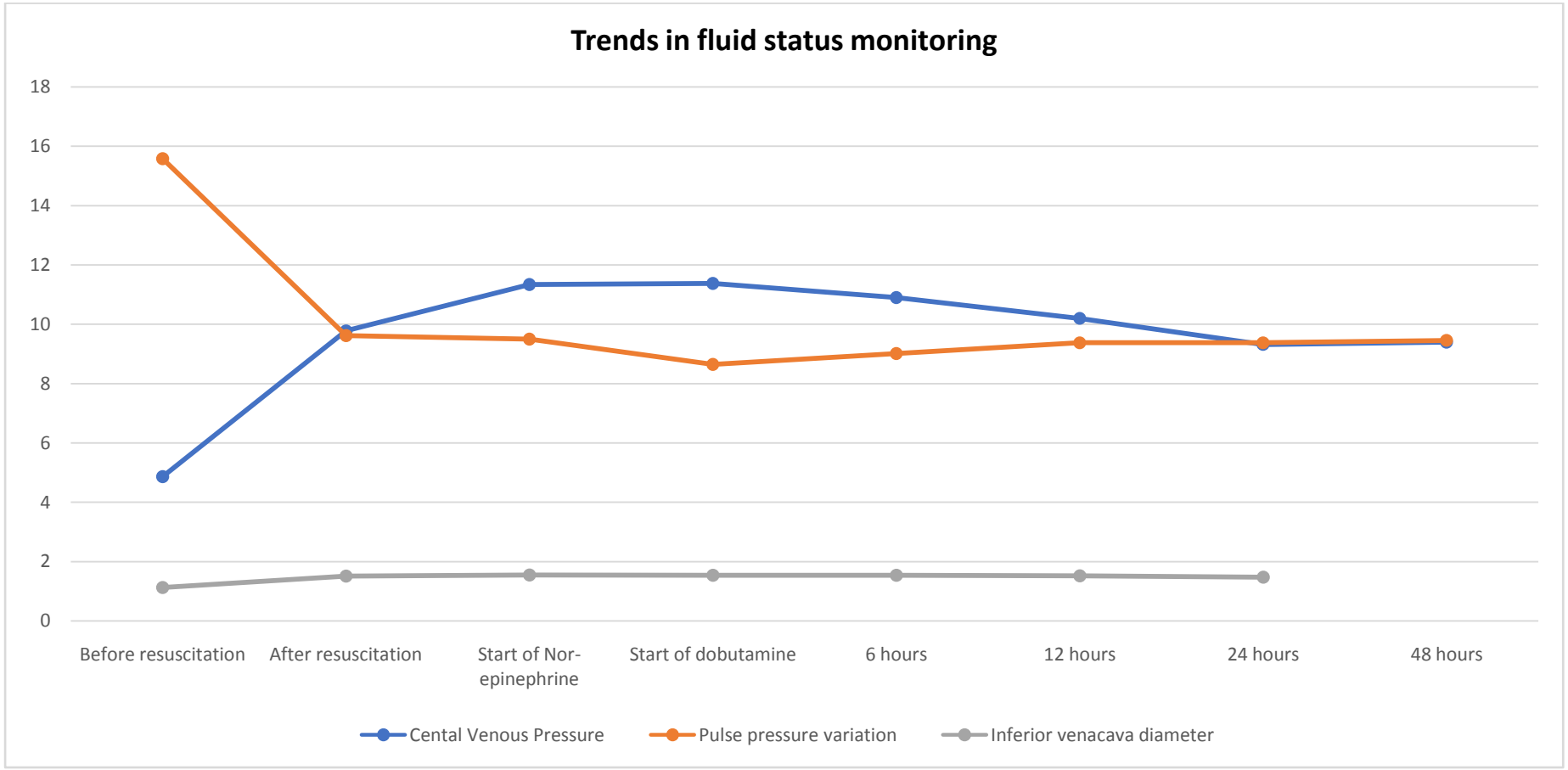
Table 10. Trends of PPV at different time points of the study

Pulse pressure variation (%)	Mean	Std. Deviation	p-value	Mean Difference	Std. Error	95% Confidence Interval for Difference	
						Lower Bound	Upper Bound
Before resuscitation	15.58	3.14					
After resuscitation	9.62	2.23					
Start of Nor-epinephrine	9.50	3.20					
Start of dobutamine	8.65	3.46	0.091	0.85	0.49	-0.14	1.84
6Hours	9.02	2.49	0.223	0.48	0.39	-0.30	1.26
12Hours	9.38	2.69	0.794	0.12	0.46	-0.80	1.04
24Hours	9.38	2.60	0.806	0.12	0.49	-0.86	1.10
48Hours	9.46	2.62	0.942	0.04	0.55	-1.06	1.14

Table 11. Trends of IVC diameter at different time points of the study

Inferior venacava diameter (cm)	Mean	Std. Deviation	p-value	Mean Difference	Std. Error	95% Confidence Interval for Difference	
						Lower Bound	Upper Bound
Before resuscitation	1.13	0.21					
After resuscitation	1.51	0.16					
Start of Nor-epinephrine	1.55	0.24					
Start of dobutamine	1.54	0.20	0.441	0.02	0.02	-0.03	0.06
6 Hours	1.54	0.16	0.658	0.02	0.04	-0.06	0.10
12 Hours	1.52	0.15	0.379	0.03	0.04	-0.04	0.11
24 Hours	1.48	0.13	0.041	0.08	0.04	0.00	0.15
48 Hours	1.52	0.15	0.393	0.04	0.04	-0.05	0.12

Figure 14. Trends of fluid status monitoring at different time points of the study



Trends in s.lactate and renal resistive index monitoring:

There is a statistically significant decrease (p= 0.01) in s.lactate and RRI values at all time points following the start of dobutamine.

Table 12. Trends of serum lactate levels at different time points of the study

s.Lactate (mmol/dl)	Mean	Std. Deviation	p-value	Mean Difference	Std. Error	95% Confidence Interval for Difference	
						Lower Bound	Upper Bound
Before resuscitation	7.13	2.61					
After resuscitation	5.85	1.98					
Start of nor-epinephrine	6.07	2.09					
Start of dobutamine	5.54	2.27	0.010	0.54	0.20	0.13	0.94
6 Hours	5.13	2.08	0.001	0.94	0.25	0.45	1.44
12Hours	4.45	1.61	0.001	1.63	0.24	1.15	2.10
24Hours	3.55	1.37	0.001	2.53	0.27	1.98	3.07
48Hours	2.75	1.28	0.001	3.32	0.31	2.69	3.95

Table 13. Trends of Renal resistive Index at different time points of the study

Renal resistive index	Mean	Std. Deviation	p-value	Mean Difference	Std. Error	95% Confidence Interval for Difference	
						Lower Bound	Upper Bound
Before resuscitation	0.75	0.05					
After resuscitation	0.72	0.04					
Start of nor-epinephrine	0.72	0.05					
Start of dobutamine	0.72	0.04	0.821	0.00	0.01	-0.01	0.02
6 Hours	0.69	0.07	0.004	0.03	0.01	0.01	0.05
12 Hours	0.66	0.07	0.001	0.07	0.01	0.04	0.09
24 Hours	0.64	0.06	0.001	0.08	0.01	0.06	0.10
48 Hours	0.61	0.05	0.001	0.11	0.01	0.10	0.13

Figure 15. Trends of serum lactate levels at different time points

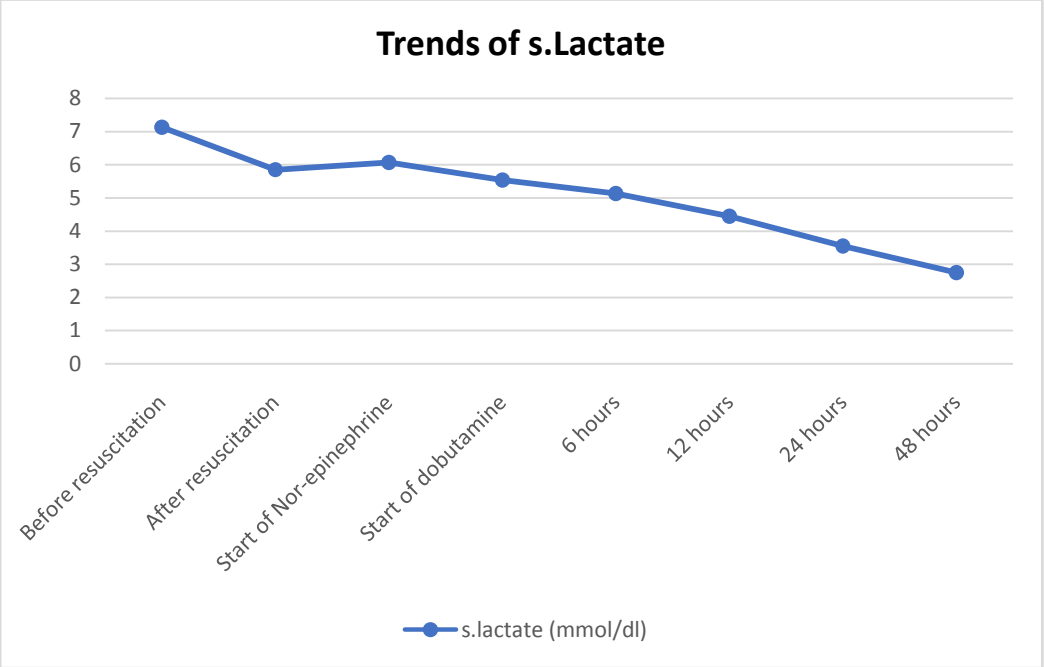
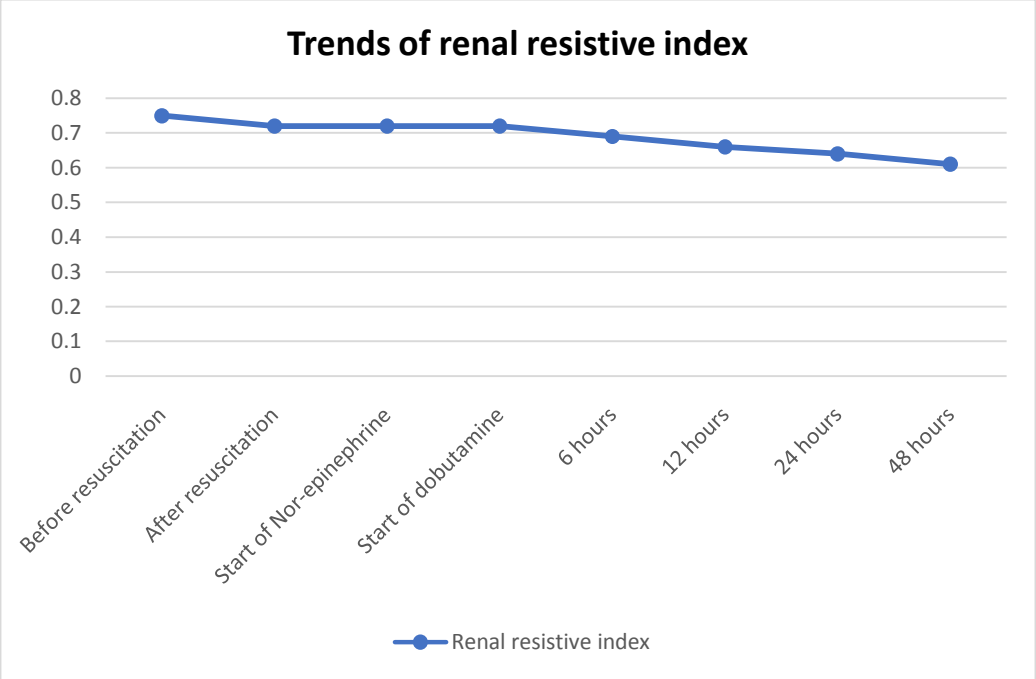


Figure 16. Trends of renal resistive index at different time points



Trends of RRI in those who received vasopressin:

There was no statistically significant difference in RRI among those patients who received vasopressin and those who did not receive vasopressin at all time points except at 24 hours.

Table 14. Trends of RRI in patients who received vasopressin

DOSE OF VASOPRESSIN	Yes		No			
RRI	Mean	SD	Mean	SD	Z	p-value
6Hour	0.71	0.07	0.69	0.07	0.757	0.453
12Hour	0.68	0.07	0.65	0.07	1.309	0.197
24Hour	0.68	0.05	0.63	0.06	2.504	0.016
48Hour	0.64	0.00	0.60	0.06	0.891	0.378

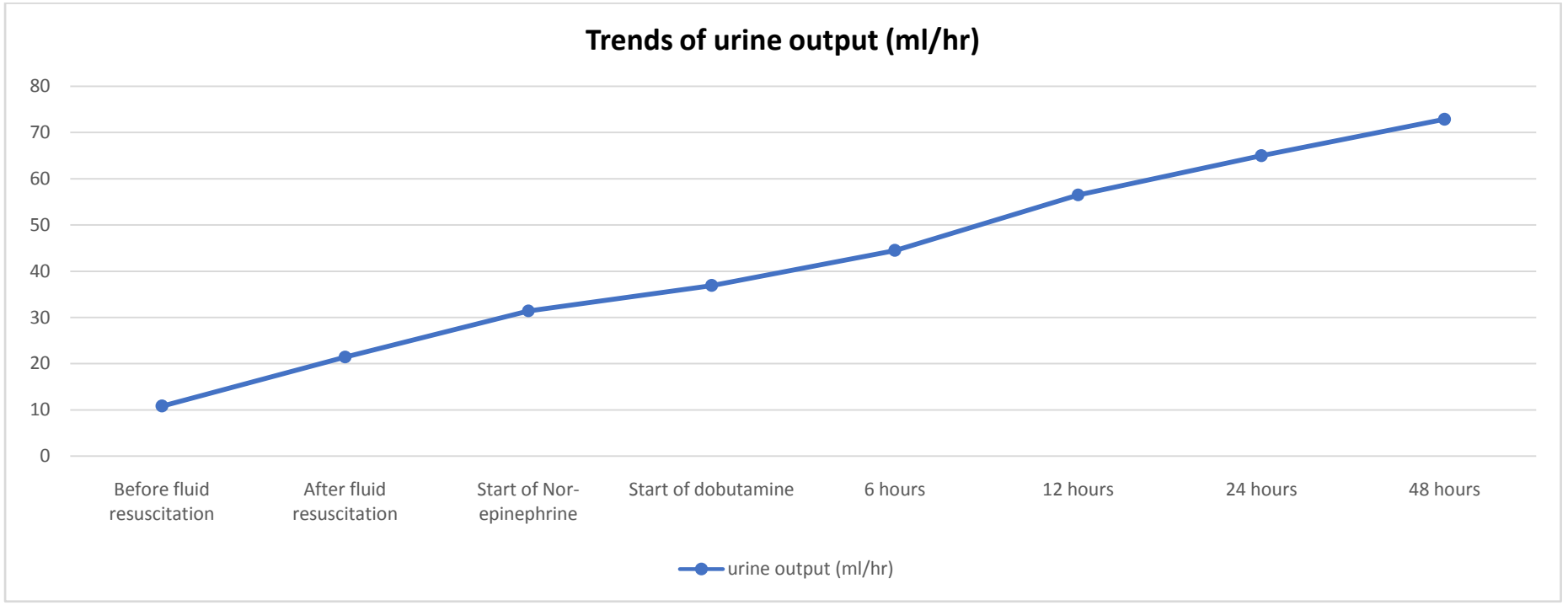
Trends in renal function following the start of ionotropic support:

There is a statistically significant increase (p= 0.001) in urine output at all time points after the start of dobutamine.

Table 15. Trends of urine output at different time points of the study

Urine output (ml/hr)	Mean	Std. Deviation	p-value	Mean Difference	Std. Error	95% Confidence Interval for Difference	
						Lower Bound	Upper Bound
Before fluid resuscitation	10.80	9.333					
After fluid resuscitation	21.40	12.166					
Start of Nor-epinephrine	31.40	11.608					
Start of dobutamine	36.90	15.81	0.008	-5.50	1.99	-9.49	-1.51
6 hours	44.50	20.08	0.001	-13.10	2.54	-18.20	-8.00
12hours	56.50	21.22	0.001	-25.10	2.56	-30.25	-19.95
24 hours	65.00	14.81	0.001	-33.60	2.33	-38.27	-28.93
48 hours	72.90	16.32	0.001	-41.50	2.70	-46.93	-36.07

Figure 17. Trends of urine output at different time points



There is a significant increase in s.urea on day 2 (p= 0.001) and day 3 (p= 0.035) as compared to day 1 of septic shock. There is also a significant raise in s.creatinine on day 2 (p=0.001) and day 3 (p= 0.001) as compared to day 1 of septic shock.

Table 16. Trends of serum urea levels at different time points of the study

s.Urea (mg/dl)	Mean	Std. Deviation	p-value	Mean Difference	Std. Error	95% Confidence Interval for Difference	
						Lower Bound	Upper Bound
Day 1	46.46	28.61					
Day 2	53.06	31.14	0.001	-6.60	1.44	-9.50	-3.70
Day 3	52.66	32.32	0.035	-6.20	2.85	-11.93	-0.47

Table 17. Trends of serum creatinine levels at different time points of the study

s.Creatinine (mg/dl)	Mean	Std. Deviation	p-value	Mean Difference	Std. Error	95% Confidence Interval for Difference	
						Lower Bound	Upper Bound
Day 1	1.39	0.88					
Day 2	1.58	0.91	0.001	-0.20	0.03	-0.26	-0.13
Day 3	1.59	1.01	0.001	-0.20	0.04	-0.28	-0.13

Figure 18. Trend of serum urea levels at different time points

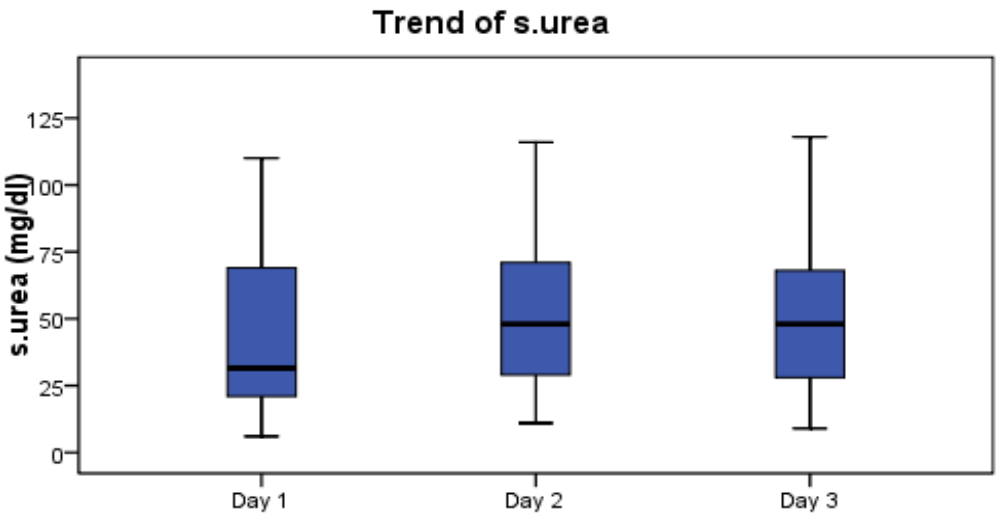
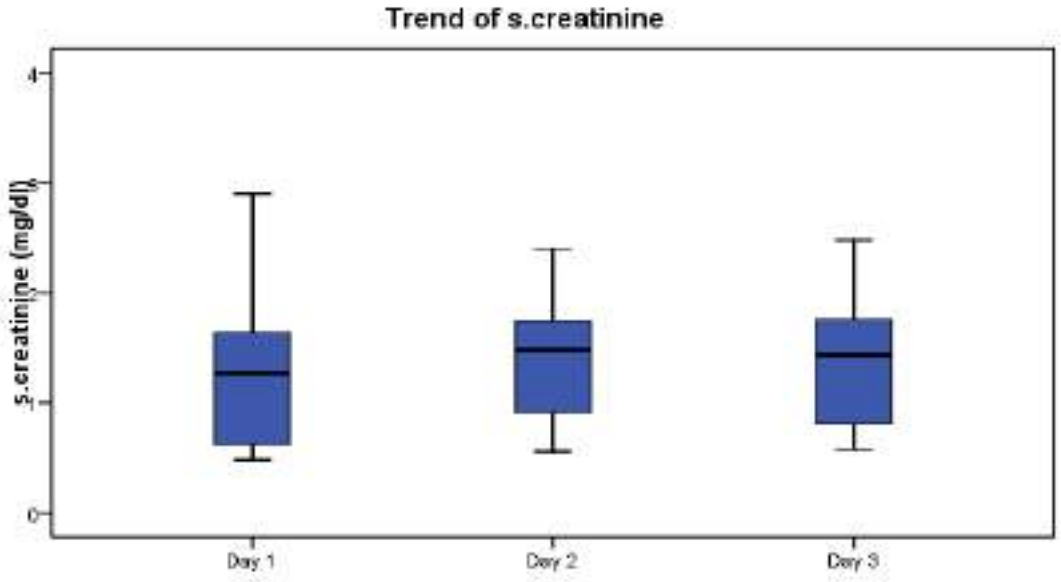


Figure 19. Trend of serum creatinine levels at different time points



Trends of Sofa score during study period:

There is a significant decrease in SOFA score on day 2 (p= 0.001) and day 3 (p= 0.001) as compared to day 1 of septic shock.

Table 18. Trends of SOFA score at different time points of the study

SOFA score	Mean	Std. Deviation	p-value	Mean Difference	Std. Error	95% Confidence Interval for Difference	
						Lower Bound	Upper Bound
Day 1	9.94	2.09					
Day 2	7.60	2.18	0.001	2.34	0.12	2.11	2.57
Day 3	6.80	2.34	0.001	3.14	0.18	2.78	3.50

There is no significant difference in ejection fraction on day 2 (p= 0.096) but there is a significant difference in ejection fraction on day 3 (p= 0.029) as compared to day 1 of septic shock.

Table 19. Trends of Ejection fraction at different time points of the study

Ejection Fraction	Mean	Std. Deviation	p-value	Mean Difference	Std. Error	95% Confidence Interval for Difference	
						Lower Bound	Upper Bound
Day 1	47.74	16.35					
Day 2	48.20	15.59	0.096	-0.46	0.27	-1.01	0.09
Day 3	48.24	15.51	0.029	-0.50	0.22	-0.95	-0.05

Figure 20. Trends of SOFA score at different time points

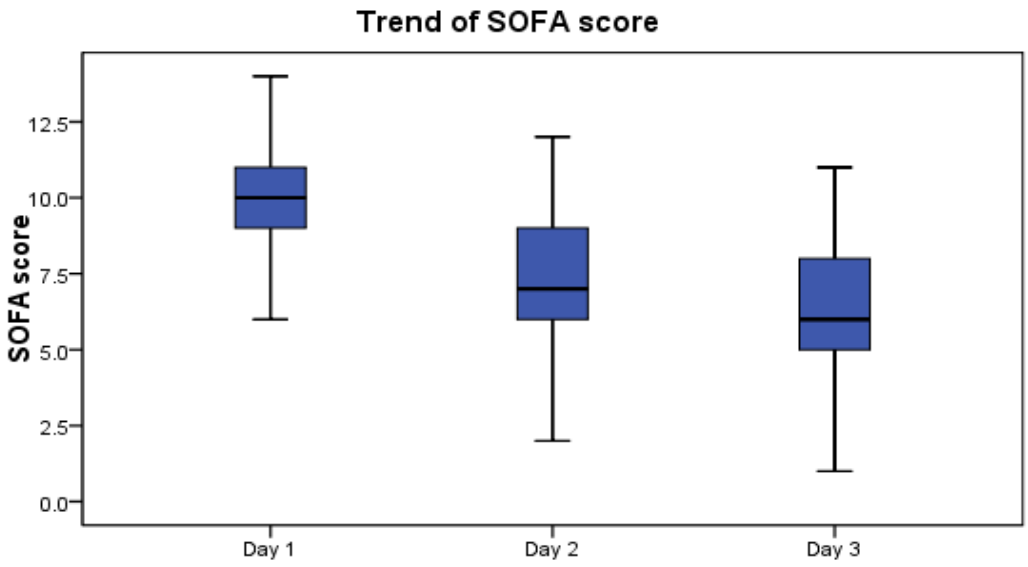
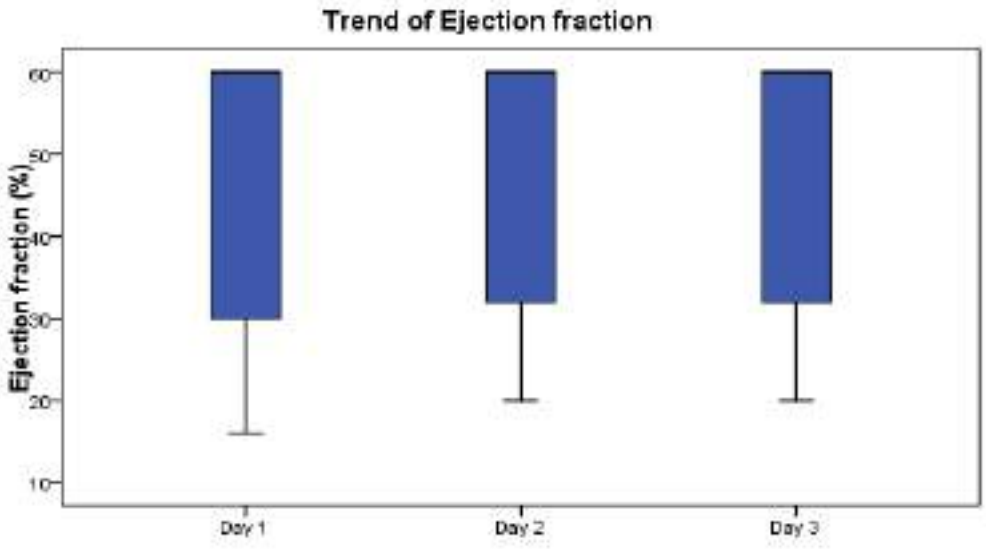


Figure 21. Trends of Ejection fraction at different time points



Correlation between s.lactate levels and renal resistive index:

Table 20. Correlation between serum lactate and renal resistive index at different time points of the study

s.lactate		RRI
Before fluid resuscitation	Pearson Correlation	-0.081
	Sig. (2-tailed)	0.575
	N	50
After fluid resuscitation	Pearson Correlation	0.131
	Sig. (2-tailed)	0.365
	N	50
At start of Nor-epinephrine	Pearson Correlation	-0.303
	Sig. (2-tailed)	0.033
	N	50
At start of Dobutamine	Pearson Correlation	-0.039
	Sig. (2-tailed)	0.788
	N	50
At 6 hours	Pearson Correlation	-0.033
	Sig. (2-tailed)	0.819
	N	50
At 12 hours	Pearson Correlation	-0.073
	Sig. (2-tailed)	0.614
	N	50
At 24 hours	Pearson Correlation	0.362
	Sig. (2-tailed)	0.010
	N	50
At 48 hours	Pearson Correlation	0.101
	Sig. (2-tailed)	0.485
	N	50

Correlation between serum lactate and RRI at different time points of the study

Figure 22. Before fluid resuscitation

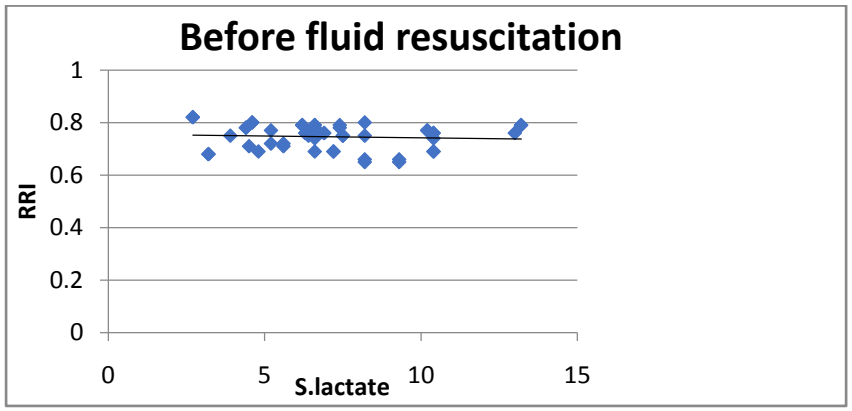


Figure 23. After fluid resuscitation

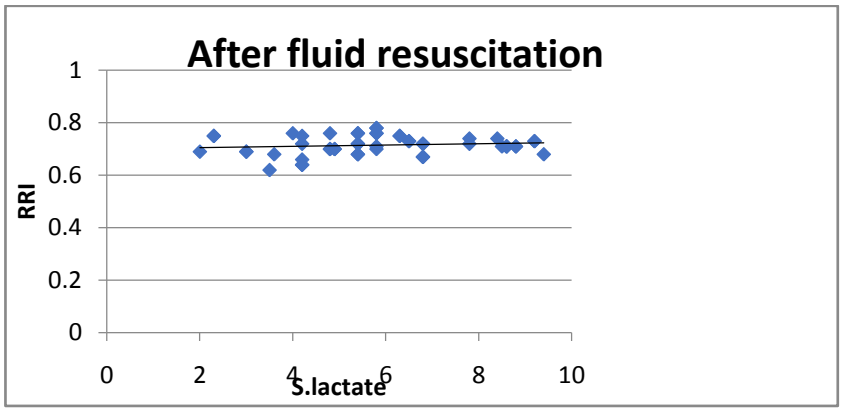


Figure 24. Start of Nor-epinephrine

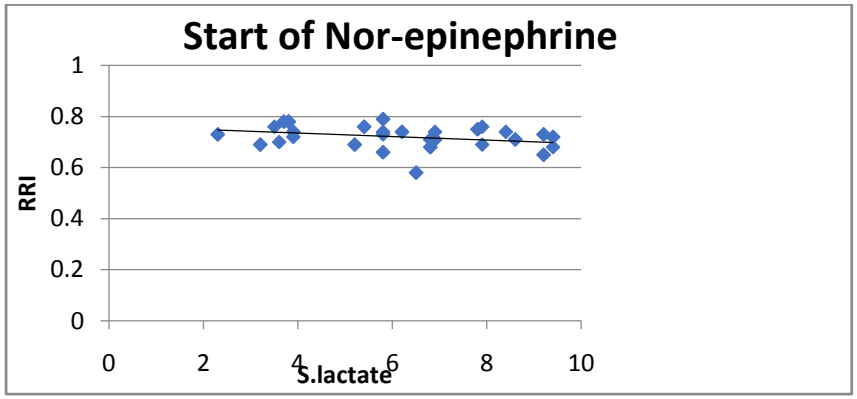
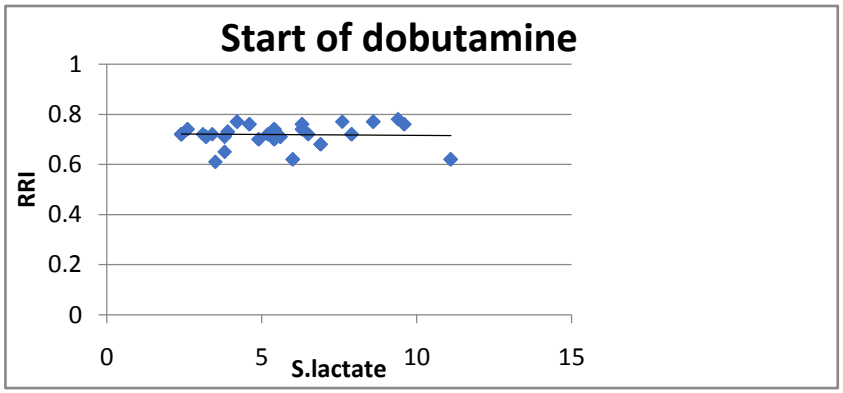


Figure 25. Start of dobutamine



Correlation between serum lactate and RRI at different time points of the study

Figure 26. At 6 hours

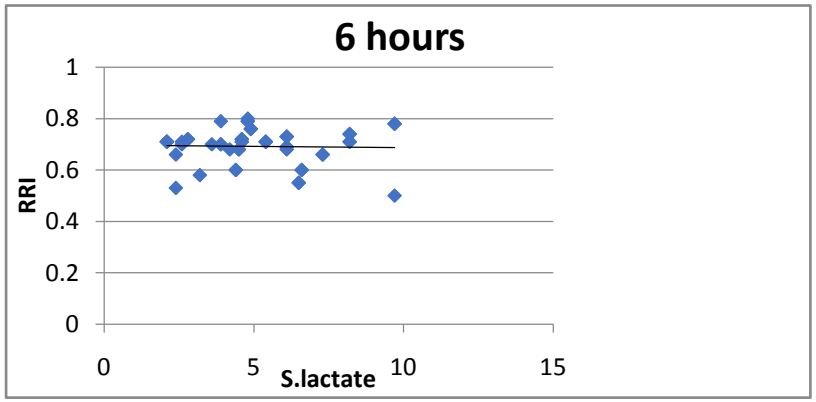


Figure 27. At 12 hours

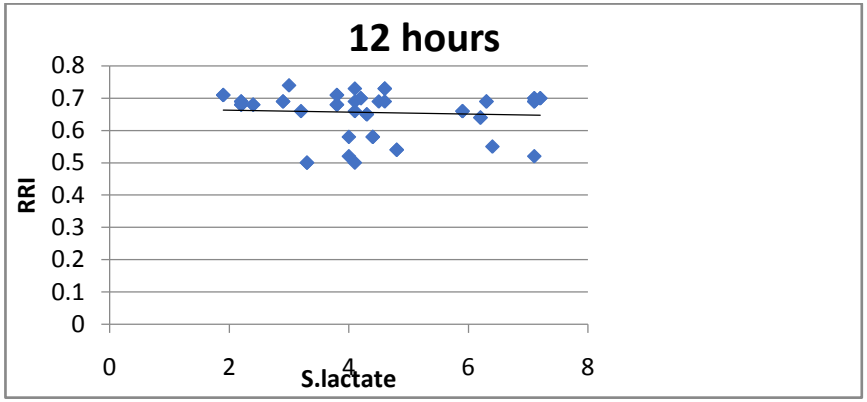


Figure 28. At 24 hours

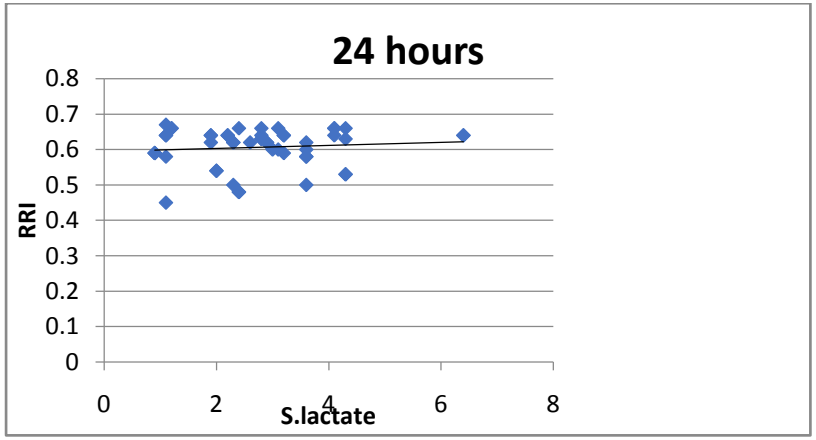
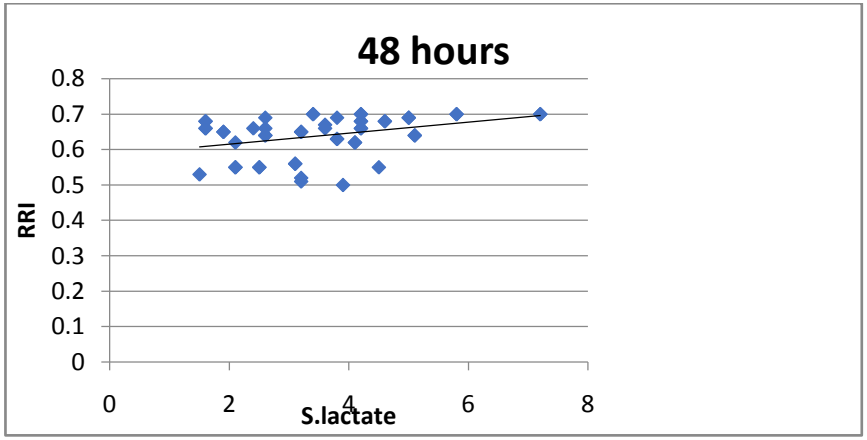


Figure 29. At 48 hours



Acute kidney Injury and Renal resistive index:

A total number of 34 (68%) patients developed acute kidney injury. Among them 18 (36%) patients developed stage 1 AKI, 7 (14%) patients developed stage 2 AKI, 9 (18%) patients developed stage 3 AKI.

Table 21. Acute Kidney injury Staging

AKI staging	No. of cases	Percentage
1	18	36.0%
2	7	14.0%
3	9	18.0%
No AKI	16	32.0%
Total	50	100.0%

Renal resistive index for patients without AKI and patients developing AKI

There is no significant change (p> 0.05) in renal resistive index in patients with acute kidney injury as compared to those without acute kidney injury.

Table 22. Relationship between RRI and AKI at different time points of the study

Renal resistive index	No AKI		AKI		Z	p-value
	Mean	SD	Mean	SD		
Before fluid resuscitation	0.73	0.06	0.75	0.04	-1.332	0.189
After fluid resuscitation	0.71	0.04	0.72	0.04	-0.665	0.509
At start of Nor-epinephrine	0.71	0.04	0.73	0.05	-1.135	0.262
At start of Dobutamine	0.72	0.04	0.72	0.05	-0.423	0.674
At 6 hours	0.68	0.05	0.70	0.08	-0.504	0.617
At 12 hours	0.64	0.07	0.66	0.07	-1.232	0.224
At 24 hours	0.63	0.06	0.64	0.06	-0.981	0.331
At 48 hours	0.60	0.06	0.61	0.05	-0.713	0.479

Figure 30: ROC curve of pre resuscitation RRI for AKI

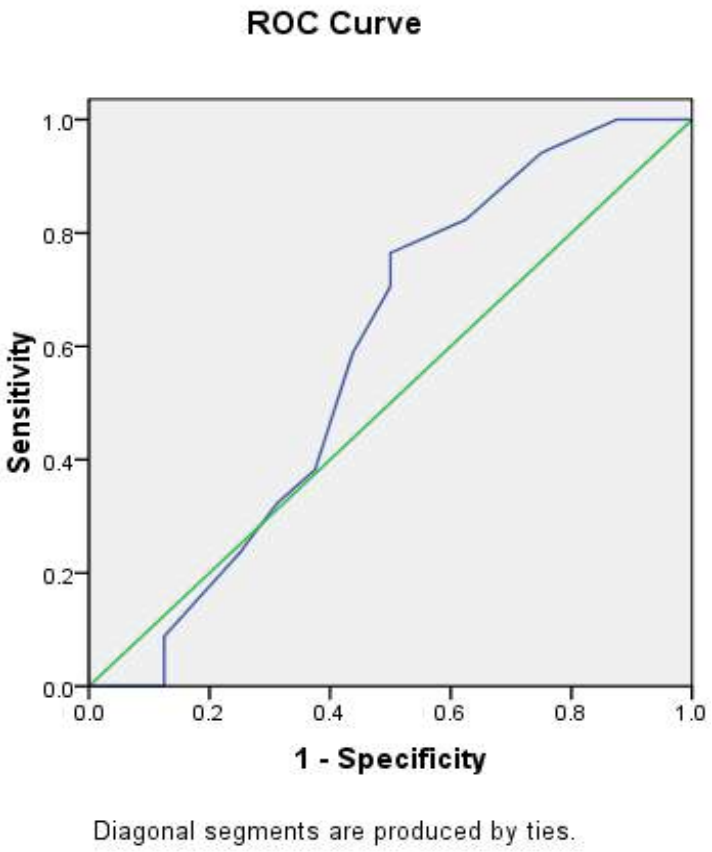


Table 23. Area Under the Curve for pre resuscitation RRI and AKI

Test Result Variable(s):Before resuscitation RRI

			Asymptotic 95% Confidence Interval	
Area	Std. Error	p-value	Lower Bound	Upper Bound
0.586	0.098	0.328	0.395	0.778

The ROC curve of RRI before resuscitation showed a poor discrimination of AKI development on day 3 versus non-AKI. Area under the curve (AUC) of RRI for was 0.586 (0.488-0.684, 95%CI 0.395-0778), p= 0.328.

28- day mortality of the patients:

A total number of n=17(34%) patients expired within 28 days of admission.

Table 24. 28-day mortality of the study population

28-D MORTALITY	No. of cases	Percentage
No	33	66.0%
Yes	17	34.0%
Total	50	100.0%

DISCUSSION

Sepsis is a life-threatening systemic immune response to infectious process which can lead to organ dysfunction and a major threat to life. More than 30 million people are being affected by sepsis with a mortality rate estimated to be as high as 6 million every year.[30]Septic shock is diagnosed if there is persistent hypotension with MAP < 65mm Hg with serum lactate level >2 mmol/dl despite adequate initial fluid resuscitation.[2,5] Shock is a severe condition and can result in vital organ injury. Hence, early and effective treatment of shock is of paramount importance.[9] According SSC 2021 update, fluid resuscitation with crystalloids should be initiated immediately in patients of sepsis with hypotension and/or elevated lactate levels. If hypotension still persists, Nor-epinephrine is the first vasopressor of choice (strong recommendation, moderate quality evidence) to maintain a MAP >65 mmHg followed by vasopressin and then epinephrine. Dobutamine is suggested in patients with evidence of persistent hypoperfusion despite adequate fluid resuscitation and use of vasopressor support as the end point of adequate resuscitation is always organ perfusion. [2,5]

Although vasopressor support reverses hypotension but it does not always ensure adequate organ perfusion. Hence, a clinical marker for organ perfusion is crucial for management of septic shock. Serum lactate is used as a surrogate marker for organ perfusion according to SSC guidelines. However, serum lactate may be elevated in conditions other than septic shock such as hepatic failure, renal failure, myeloproliferative disease, pancreatitis, short bowel syndrome, hypoxia, anemia, regional ischemia and drugs such as catecholamines, biguanides, methanol, ethanol and ethylene glycol. Hence, a more specific indicator of hypoperfusion is needed to guide the therapy. [2,6]

Kidney is the most commonly affected organ in septic shock due to hypoperfusion with an incidence of 25% in patients with sepsis and 50% in patients with septic shock in ICU. Although many markers such as neutrophil gelatinase-associated lipocalin, tissue inhibitor of

metalloprotease-2, kidney injury molecule-1 are known to assess AKI and have proven benefit but are not cost-effective. However, bedside ultrasound Doppler of renal vessels is a noninvasive, easily accessible, repeatable tool which gives a real time monitoring of renal perfusion. Renal resistive index (RRI) measured by doppler ultrasound is a sonographic index of alterations in blood flow within the arcuate arteries or interlobar arteries of kidney. Muller et al, in his prospective observational study on RRI as an early predictor of AKI concluded that high RRI on ICU admission was a significant predictor for development of AKI stage 2-3 during the first week.[9,15]

The major objective of our study was to evaluate the effect of dobutamine on RRI as a measure of organ hypoperfusion and to use RRI as a surrogate marker of organ hypoperfusion as kidney is one of the most commonly affected organ in septic shock.

This was a prospective observational study conducted in septic shock patients admitted to intensive care units of the hospital during a period of 19 months (March 2020 to November 2021). A total number of 329 septic shock patients were assessed but 206 patients did not meet inclusion criteria, 48 patients did not give consent, 19 patients required CRRT during the study period, 4 patients expired during the study period, 2 patients could not be followed for 28 days and hence, 50 patients were finally analyzed for the study. Majority of the patients were males (64%) with a mean age of 48.16±15 years. While majority (62% patients) were post-operative patients with sepsis, and abdomen was the most common source of infection (46%). Gram negative bacteria was isolated in 76% of the study population. Diabetes mellitus was the most commonly associated co-morbid condition affecting 34% individuals. The mean SOFA score on ICU admission was 9.76±2.24 and mean hematocrit was 11.34±2.08% (Table 1 & 2).

Patients with septic shock were initially resuscitated according to surviving sepsis campaign guidelines with 30ml/kg crystalloids and the fluid status was monitored using parameters such as PPV, IVC diameter and CVP. There was a significant improvement in vital parameters. The mean decrease in heart rate was of 15.6 beats per

minute and MAP increased by a mean difference of 10 mmHg following resuscitation (p= 0.001) which is significant (Table 3). This was in concordance with previous study by Guarracino et al, comparing the cardiovascular determinants before and after resuscitation with 30ml/kg crystalloids where mean heart rate decreased by 17 beats per minute and MAP increased by 10 mm Hg.[31]

There was also a significant difference (p= 0.001) in hemodynamic monitoring parameters such as PPV, IVC diameter and CVP before and after resuscitation. The mean PPV was decreased by 6%, the mean IVC diameter was increased by 4mm and mean CVP increased by 5 cm of H_2O (Table 3). This was also in concordance with the study by Guarracino et al, where mean PPV was decreased by 4.5%.[31]

There was also a significant difference (p= 0.001) in metabolic parameters following fluid resuscitation such as serum lactate decreased by 1.2mmol/dl (p= 0.001) and renal parameters such as RRI decreased from 0.75 to 0.72 (p= 0.001) and urine output increased by 11ml/hour (p= 0.001) following resuscitation (Table 3). Similar effects were observed in a study conducted by Moussa et al., who studied the effect of fluid administration on renal perfusion and observed that fluid administration resulted in decrease in RRI from 0.73 to 0.71 with concomitant increase in MAP, 6% decrease in PPV and 26 ml/hr increase in urine output. Our observation and results are similar to these findings.[32]

Nor-epinephrine infusion was started if there was persistent hypotension despite fluid resuscitation. In our study, the mean dose of Nor-epinephrine was 0.21±0.06 µg/kg/min. After achieving a of MAP >65 mm Hg, a low dose dobutamine (2-5µg/kg/min) was added.[32] In our study, there was a significant improvement in hemodynamics after starting dobutamine at all time points, as observed by significant (p= 0.001) decrease in heart rate and increase in MAP (p= 0.001). The dose of nor-epinephrine significantly increased (p= 0.001) initially after start of dobutamine but later on decreased over 2 days (Table 4). In a study by Enrico et al, use of dobutamine at a dose of 10µg/kg/min in

septic shock patients demonstrated a significant (p< 0.00001) increase in heart rate with no change in mean arterial pressure (p= 0.31) along with an increase in Nor-epinephrine dose (Table 7 & 8). These results are contradictory to our observation and can be explained by the low dose of dobutamine (5µg/kg/min) used in our study which was further tapered with improvement in organ function as measured by decrease in serum lactate, decrease in RRI and improvement in urine output. Also, this could be due to the additional effect of stabilization of the patients with sedation in those mechanically ventilated patients and antipyretics. In our study there was a significant increase in MAP when dobutamine was started which is also in contrast with previous study by Enrico et al, who observed no increase in mean arterial pressure. This difference can be explained that immediately after starting dobutamine, reflex reduction in sympathetic tone in response to augmentation of stroke volume can led to decrease in the total peripheral resistance which resulted in significant increase in dose of Nor-epinephrine. As organ perfusion improved over time with dobutamine use, requirement of nor-epinephrine at all time points of observation following start of dobutamine significantly decreased.[25]

There was no significant difference (p value >0.05) in PPV and IVC diameter following the start of ionotropic support at all time points over 48 hours as the fluid status was guided based on these parameters and resuscitated accordingly (Table 10 & 11). There was a significant decrease (p= 0.001) in serum lactate levels after the start of dobutamine (Table 12). Previous studies also demonstrated a decrease in serum lactate levels after the start of dobutamine in addition to nor-epinephrine. In a study conducted by Mahmoud et al, Nor-epinephrine supplemented with dobutamine group of patients demonstrated a significant decrease in serum lactate levels (p= 0.04).[21] The decrease in serum lactate with the use of dobutamine was also reported in study done by Durantea et al, and they attributed this finding to action on β2 receptors which has a vasodilatory effect and improves the splanchnic blood flow and decreases the regional increase in lactate levels.[33]

The most important finding of our study was the significant decrease (p= 0.001) in RRI accompanied by significant increase in urine output at all time points (p= 0.001) following initiation of dobutamine in patients with septic shock (Table 13 & 14) Although the effect of dobutamine on RRI has not yet described in literature and to the best of our knowledge there is no evidence available on the effect of dobutamine on RRI however, in a study conducted by Deruddre et al, on the effect of increasing MAP on RRI revealed that on increasing MAP from 65 to 75 mm Hg, RRI significantly decreased from 0.75 to 0.71 and urine output significantly increased from 76 to 93ml/hr. However, no difference was found when MAP was increased from 75 mm Hg to 85 mm Hg.[34] Thus, improvement in RRI and urine output in our patients can be explained by dual effect. Firstly, that Dobutamine by reducing after-load as well as through its inotropic action improves CO and hence, renal perfusion.[35]Secondly, effects of dobutamine on renal sympathetic activity is associated with increases in renal blood flow (RBF) (11%) and glomerular filtration rate (GFR) (12%) as have been described by Al-Hesayen A et al, that Dobutamine exerts vasodilator effects on both afferent and efferent arterioles and increases RBF.[36]

However, there was a significant increase (p= 0.001) in renal function test as measured by serum urea and creatinine in our septic shock patients following use of vasopressors (Table 16 &17). As it is known that injury to the kidney has already occurred before these renal markers become deranged. This time lag explains that the rise in urea and creatinine in our patients could be due to the effect of sepsis itself or initial insult caused by shock prior to resuscitation. Another explanation can be sepsis induced catabolic activity. This is supported by a study conducted by Doi et al, in postoperative sepsis patients on the predictive value of creatinine on acute kidney injury. [37]

They found that acute changes in creatinine lag behind both renal injury and recovery. This has led to the search of novel biomarkers like NGAL. KIM-1, interleukin 18 (IL-18), cystatin C as tools for early detection of AKI especially in septic patients

In our study there was a significant improvement (p= 0.001) in SOFA score on day 2 and day3 as compared to baseline, from mean SOFA score of 9.94±2 to 6.8±2.34 in septic shock patients with improvement in hemodynamics and renal parameters (Table 18). Similar findings were observed in a study conducted by Mahmoud et al, who compared the effect of norepinephrine supplemented with either epinephrine or dobutamine for cardiovascular support in patients with septic shock. They reported that time to hemodynamic success was 4 days and vasopressor withdrawal was 5 days and was accompanied by corresponding improvement in SOFA score. The improvement in low ejection fraction at baseline was not seen till day 2 but there was significant improvement in the ejection fraction from 41% to 57% on day 3 (p= 0.029) after starting dobutamine(Table 19). [21,24]

There is no significant correlation between serum lactate levels and RRI at all the time points in the study except at the start of Nor-epinephrine which showed a negative correlation (r= -0.3, p= 0.03), although not high (Table 20). G Fotopoulou et al. investigated the correlation of RRI on intensive care unit admission with other tissue hypo-perfusion indices and clinical outcome.[39] They concluded that renal blood flow assessed by RRI, on ICU admission, correlates with global tissue hypoperfusion indices although combination of both better predicts clinical outcome than RRI alone.[38]

In our study RRI was high in patients at baseline who later developed AKI on day 3 of septic shock, however it was not statistically significantly (p= 0.189) and AUC was o.586 (Table 22 & 23). In previous study by Muller et al, who observed that high RRI on ICU admission was an independent and significant predictor of AKI stage 2-3 during the first week of sepsis. [8] The lack of statistical significance in our study can be explained by the difference in methodology. We observed patients for 3 days as compared to Muller et al. where patients were followed for 7 days and also the sample size in our study was lower as compare to Muller et al.[8] S.creatinine is used as a biomarker for AKI staging which is only increased or decreased gradually and hence cannot be used as a marker in early stages of

AKI.[37] Hence the values of RRI could not directly correlate with s,creatinine or AKI but correlated well with urine output in our study.

28- day all-cause mortality in our study was 34% (Table 24) which is similar to the results of Annane et al. who compared Norepinephrine plus dobutamine versus epinephrine alone in management of septic shock. In their study all cause 28-day mortality was also 34%.[24] However, Mahmoud et al, reported a higher the all-cause mortality in Nor-epinephrine with dobutamine supplemented group was 50%.[21]

Strengths and limitations of the study:

In our study patient acted as their own control, as dobutamine effect on RRI was compared with baseline RRI after resuscitation. This can be advantageous as patient served as their own control but drawback is that we did not compare with placebo. Despite this, the different response of the study population following the start of norepinephrine and start of dobutamine allowed us to compare separate responses and their determinants.

1. Although renal resistive is an easy bed side non-invasive tool to predict renal function in an acute setting, but it cannot used as a tool in patients on renal replacement therapy (RRT), renal artery stenosis, chronic kidney disease, cirrhosis with hepatorenal syndrome, use of renin-angiotensin-aldosterone antagonists and pregnancy. Hence, there were many exclusion criteria limiting the number of study participants.
2. Confounding factors such as effect of drugs other than ionotropes which influence renal perfusion were not identified in this study that could have influenced the results.
3. There can be wide inter as well as intra observer variation in RRI measurements, however in our study RRI was noted by only one observer and mean of 3 measurements were taken into consideration.
4. Also, RRI and cardiac assessment were static and periodic.
5. Another drawback was that 24hour urine creatinine clearance and eGFR was not calculated to estimate AKI

SUMMARY AND CONCLUSION

The present observational study was conducted on patients of septic shock admitted in Intensive care units of the hospital. The major objective of the study was to evaluate the effect of dobutamine on RRI in septic shock patients. The secondary objectives were to determine the correlation between serum lactate levels and RRI as well as to assess the relationship between RRI and AKI. After obtaining approval from institutional Ethics Committee, 50 patients were analyzed in this study.

Majority of the patients were males (64%) with a mean age of 48.16±15 years. While majority (62%) were post-operative patients, with sepsis, with abdomen being the most common source of infection, in 46% patients. There was a significant improvement in vital parameters (HR, MAP) and hemodynamic parameters (PPV, CVP and IVC diameter) following initial fluid resuscitation. There was also significant improvement in serum lactate, RRI and urine output following initial fluid resuscitation.

In our study, there was a significant improvement in hemodynamics after starting dobutamine at all time points , as observed by significant (p= 0.001) decrease in heart rate and increase in MAP (p= 0.001). The dose of nor-epinephrine significantly increased initially after start of dobutamine but later on decreased over 2 days (p= 0.001). There was no significant change in PPV and IVC diameter following start of Nor-epinephrine.

There was a significant decrease (p= 0.001) in RRI after starting dobutamine infusion. There was also significant improvement in serum lactate levels and urine output following dobutamine infusion. However, there was no significant correlation between serum lactate levels and RRI values at all time points over 48 hours. There was a significant rise (p= 0.001) in serum creatinine levels on day 2 and day 3. However, there was no relationship between initial RRI measurement following septic shock and development of AKI on day 3.

In our study there was a significant improvement in SOFA score (p= 0.001) and ejection fraction (p= 0.029) over 48 hours compared to baseline. 28- day all-cause mortality in our study was 34%.

Hence, our study concludes that with dobutamine infusion in patients of septic shock there was a significant decrease in renal resistive index, which is a marker of renal perfusion. This resulted in a significant increase in urine output in these patients. However, there was no correlation between RRI and serum lactate levels. There was also no relationship between pre-resuscitation RRI values in septic shock patients who later developed of AKI on day 3.

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KEY TO MASTER CHART

SEX	
M	MALES
F	FEMALES
COMORBIDITIES	
DM	DIABETES MELLITUS
HTN	HYPERTENSION
TB	TUBERCULOSIS
CAD	CORONARY ARTERY DISEASE
Y	YES
N	NO
DIAGNOSIS	
AFI/TCP	ACUTE FERBRILE ILLNESS WITH THROBOCYTOPENIA
LRTI	LOWER RESPIRATORY TRACT INFECTION
UTI	URINARY TRACT INFECTION
ABD TB	ABDOMINAL TUBERCULOSIS
BKA	BELOW KNEE AMPUTATION
HSV ENCEPHALITIS	HERPES SIMPLEX VIRUS ENCEPHALITIS
COPD WITH AE	CHRONIC OBSTRUCTIVE PULMONARY DISEASE WITH ACUTE EXACERBATIONS
GJ	GASTRO JEJUNOSTOMY
RT	RIGHT

S.No.	NAME	AGE	SEX	MRD	WEIGHT	HEIGHT	DOA	DOA TO ICU	DIAGNOSIS	CO MORBIDITIES	SOFA AT ADMISSION	PARAMETERS BEFORE INITIAL FLUID RESUSCITATION								
												HR	MAP	CVP	PPV	S.LACTATE	RRI	U.O (ML/KG/HR)	IVC	HR
1	KD	59	F	1108729	63	159	2/13/2021	2/16/2021	POST COVID SEPTIC SHOCK	DM	6	160	57	3	21	6.6	0.74	10	1.1	142
2	HD	64	F	1008591	71	164	12/29/2020	12/30/2020	COPD WITH AE	HTN	9	136	63	3	16	10.2	0.77	15	1	121
3	NK	52	F	1129518	66	153	6/29/2021	6/30/2021	LIVER ABSCESS RUPTURE	DM	10	148	57	4	16	4.8	0.69	5	1.2	132
4	MS	65	M	1157631	79	174	8/19/2021	8/19/2021	FOURNIER'S GANGRENE S/P DEBRIDEMENT	DM	10	162	50	3	22	13.2	0.79	N	0.9	148
5	SK	30	M	1151441	72	173	8/10/2021	8/24/2021	PANCREATIC NECROSECTOMY	DM, OBESE	10	132	63	4	19	10.4	0.74	5	1.1	116
6	RL	48	M	1163567	90	168	8/29/2021	8/30/2021	GASTRIC PERFORATION REPAIR	OBESE	9	146	67	7	14	5.2	0.72	20	1.4	128
7	KK	24	F	1114972	63	156	5/30/2021	5/31/2021	S/P LSCS WOUND DEHISENCE	N	5	146	63	8	14	6.9	0.76	25	1.1	132
8	AS	57	M	1118347	88	172	10/11/2021	10/13/2021	PANCREATIC NECROSECTOMY	ALCOHOLIC	11	142	63	7	13	7.2	0.69	25	1.2	128
9	BS	65	M	1108729	76	174	6/14/2021	6/21/2021	DIABETIC FOOT WITH BED SORE	DM	9	126	63	10	13	6.6	0.69	15	1.3	110
10	JG	38	F	1099579	70	165	4/30/2021	4/30/2021	POST LSCS SEPTIC SHOCK	N	8	140	57	8	16	8.2	0.75	10	1.5	128
11	TC	63	M	1043981	64	159	3/7/2021	3/11/2021	DIABETIC FOOT S/P DEBRIDEMENT	DM,HTN,CAD	11	162	62	6	11	3.2	0.68	20	1.6	158
12	KK	57	M	980269	70	170	10/26/2020	11/20/2020	SUB ACUTE INTESTINAL OBSTRUCTION WITH RT HEMICOLECTOMY WITH ENTEROCUTANEOUS FISTULA	DM	5	130	63	4	18	13	0.76	5	1.02	110
13	SS	51	M	930073	70	164	5/29/2020	6/5/2020	CA STOMACH, SUB TOTAL COLECTOMY	CAD	3	120	67	4	22	3.9	0.75	5	0.9	100
14	MR	72	F	1018783	70	154	2/1/2021	2/4/2021	CHOLEDOCHOLITHIASIS, CBD EXPLORATION WITH GJ	N	9	160	57	3	19	4.5	0.71	15	1.1	138
15	KS	23	M	1005823	70	170	2/12/2021	2/19/2021	ABD TB WITH ILEOSTOMY	TB	9	160	48	1	10	2.7	0.82	N	0.6	140
16	RK	30	F	1171877	65	165	9/12/2021	9/13/2021	HSV ENCEPHALITIS	N	14	162	67	3	20	10.4	0.76	10	1	144
17	JS	40	M	1128358	70	168	6/27/2021	6/30/2021	POST COVID FUNGAL SEPSIS	DM	8	130	67	4	14	6.3	0.76	10	1.2	110
18	SD	45	F	1101337	65	163	5/2/2021	5/2/2021	ACUTE PANCREATITIS	N	10	145	67	4	16	6.4	0.75	15	1.1	132
19	SK	51	M	778301	74	166	3/11/2021	3/11/2021	POST COVID SEPTIC SHOCK	HTN,CAD	11	143	62	2	18	7.4	0.78	N	1.3	126
20	CS	48	M	920880	78	174	3/31/2020	4/4/2020	FOURNIER'S GANGRENE S/P DEBRIDEMENT	N	9	140	63	2	12	8.2	0.65	25	0.9	122
21	PCG	69	M	852929	70	168	8/18/2020	8/22/2020	PERFORATION PERITONITIS S/P RESECTION	DM, HTN	14	130	62	6	14	7.5	0.75	15	1.1	110
22	RK	44	M	1029355	75	155	12/13/2020	12/13/2020	PANCREATIC NECROSECTOMY	ALCOHOLIC	12	152	57	4	18	4.4	0.78	N	0.9	138
23	GK	55	F	1049834	62	153	4/19/2021	4/23/2021	PANCREATIC NECROSECTOMY	N	10	168	57	2	12	6.6	0.79	N	1.2	156
24	AK	23	F	1079461	84	173	4/7/2021	4/8/2021	S/PCHOLECYSTECTOMY	N	11	160	63	4	18	4.6	0.8	N	1.1	146
25	HD	21	F	1034312	66	164	6/9/2021	6/21/2021	ABD TB ILEAL STRICTURE	TB	10	150	62	8	14	5.6	0.72	10	1.2	132
26	KS	60	M	1187992	80	174	10/8/2021	10/9/2021	AFI/TCP	DM,HTN	12	138	64	4	16	10.4	0.69	25	1.02	116
27	BS	40	M	1187349	82	172	10/7/2021	10/7/2021	AFI/TCP	N	11	138	63	6	14	9.3	0.66	25	1.3	128
28	KK	38	F	1191390	68	161	10/15/2021	10/15/2021	UTI WITH SEPTIC SHOCK	DM	10	140	57	6	16	6.2	0.79	5	1.1	126
29	GS	28	M	1110722	72	168	6/16/2021	6/18/2021	POST COVID SEPTIC SHOCK	N	8	160	48	1	10	2.7	0.82	N	0.6	140
30	MH	66	F	1077936	69	163	4/6/2021	4/8/2021	LRTI SEPSIS	N	12	162	67	3	21	10.2	0.77	10	1	144
31	BR	66	M	1088794	66	159	4/18/2021	4/19/2021	POST COVID SEPTIC SHOCK	N	8	130	67	4	15	6.3	0.76	15	1.2	110
32	PL	55	F	1065727	76	164	3/26/2021	3/28/2021	UTI WITH SEPTIC SHOCK	DM	10	145	67	5	15	6.4	0.76	10	1.1	132
33	BR	64	F	1197290	78	176	10/25/2021	10/26/2021	LRTI SEPTIC SHOCK	N	11	143	62	2	16	7.4	0.79	N	1.3	126
34	NS	31	M	285255	69	168	7/8/2021	7/8/2021	ACUTE PANCREATITIS	N	8	146	63	3	12	8.2	0.66	25	0.9	122
35	GS	28	M	1130509	78	171	8/5/2021	8/5/2021	PANCREATIC NECROSECTOMY	N	13	130	62	6	14	7.5	0.75	10	1.1	121
36	SS	62	M	1147235	82	168	8/13/2021	8/13/2021	UTI WITH SEPTIC SHOCK	HTN	12	152	57	4	18	4.4	0.78	5	0.9	138
37	VG	48	M	1155030	75	172	8/18/2021	8/18/2021	DENGUE SHOCK	N	10	168	58	2	12	6.6	0.79	N	1.2	156
38	SG	27	M	1163578	72	168	8/29/2021	8/30/2021	CELLULITIS OF RT LEG	DM	12	158	63	5	18	4.6	0.8	N	1.1	146
39	LS	63	M	1186101	68	165	10/5/2021	10/11/2021	DUODENAL PERFORATION REPAIR	N	11	150	62	8	14	5.6	0.71	15	1	132
40	AG	28	M	1187375	78	171	10/8/2021	10/9/2021	PANCREATIC NECROSECTOMY	N	12	138	64	4	16	10.4	0.69	25	1.02	116
41	NK	52	F	1036177	72	167	2/28/2021	2/28/2021	DIABETIC FOOT S/P DEBRIDEMENT	DM,HTN	11	138	63	6	14	9.3	0.65	25	1.2	128
42	M	57	M	1071114	76	166	3/31/2021	4/10/2021	POST COVID SEPTIC SHOCK	N	10	140	57	7	16	6.2	0.79	N	1.1	126
43	BK	65	F	1075512	64	158	4/4/2021	4/10/2001	POST COVID SEPTIC SHOCK	N	10	162	50	3	22	13.2	0.79	N	0.9	148
44	RK	38	M	1084236	75	168	4/12/2021	4/15/2021	PERFORATION PERITONITIS S/P RESECTION	N	11	132	63	4	19	10.4	0.76	20	1.1	116
45	KS	60	M	1004698	67	164	5/12/2021	5/13/2021	DIABETIC FOOT	DM	8	146	62	7	14	5.2	0.77	10	1.4	128
46	AM	62	M	1120961	70	171	6/10/2021	6/11/2021	DIABETIC FOOT S/P BKA	DM	5	146	63	8	14	6.9	0.76	5	1.1	132
47	RS	33	M	1176822	73	174	9/20/2021	9/21/2021	AFI/TCP	N	11	142	63	7	13	7.2	0.69	25	1.2	128
48	AS	67	M	1183299	84	182	10/1/2021	10/1/2021	AFI /TCP/SEPTIC SHOCK	N	9	126	63	10	13	6.6	0.78	N	1.3	110
49	LR	42	M	1184281	77	175	4/2/2021	4/4/2021	DIABETIC FOOT S/P DEBRIDEMENT	DM,HTN	9	144	57	8	16	8.2	0.8	N	1.5	128
50	M	34	F	1188739	58	156	9/16/2021	7/17/2021	DENGUE WITH SEPTICSHOCK	N	11	158	64	6	11	3.2	0.68	25	1.6	158

		PARAMETERS AFTER INITIAL FLUID RESUSCITATION							0-HR OF START OF IONOTROPE								1-HR OF START OF IONOTROPE						
S.No.	NAME	MAP	CVP	PPV	S.LACTATE	RRI	U.O (ML/KG/HR)	IVC	DOSE OF NOR EPINEPHRINE µg/kg/min	HR	BP	CVP	IVC	PPV	S.LACTATE	RRI	U.O (ML/KG/HR)	DOSE OF NOREPINEPHRINE	DOSE OF DOBUTAMINE	DOSE OF VASOPRESSIN	HR	BP	CVP	IVC
1	KD	67	10	10	4.2	0.72	25	1.4	0.25	138	67	10	1.6	13	3.9	O.72	25	0.3	3	0.02	138	67	10	1.4
2	HD	73	10	7	8.4	0.74	25	1.4	0.2	128	73	12	1.4	9	8.4	0.74	30	0.2	3	N	124	77	10	1.3
3	NK	77	9	11	3.6	0.68	25	1.6	0.2	141	63	9	1.6	11	3.6	0.7	30	0.3	2	0.02	148	73	10	1.7
4	MS	63	9	11	9.2	0.73	20	1.2	0.3	142	70	9	1.7	8	9.2	0.73	40	0.3	2	0.04	138	73	10	1.6
5	SK	77	10	8	8.6	0.71	20	1.8	0.25	138	77	11	1.7	7	8.6	0.71	50	0.3	3	N	129	79	14	1.9
6	RL	73	9	12	4.8	0.7	25	1.6	0.2	138	73	10	1.5	14	3.8	0.78	30	0.2	3	N	126	70	12	1.6
7	KK	67	12	10	5.4	0.68	40	1.6	0.25	130	83	13	1.7	14	6.8	0.71	50	0.2	3	N	126	84	10	1.6
8	AS	73	10	10	6.8	0.67	30	1.5	0.25	148	67	13	1.5	8	6.8	0.68	25	0.25	3	N	136	67	12	1.4
9	BS	80	12	8	4.2	0.66	40	1.6	0.2	116	80	14	1.6	10	7.9	0.69	25	0.25	2	N	112	83	12	1.5
10	JG	67	12	12	7.8	0.72	50	1.8	0.1	130	80	14	1.2	12	7.8	0.75	50	0.1	3	N	128	93	12	1.5
11	TC	83	10	9	3	0.69	25	1.8	0.25	148	77	16	1.8	6	3.2	0.69	25	0.3	3	N	142	80	14	1.6
12	KK	77	11	6	9.4	0.68	15	1.1	0.1	130	77	16	1.1	4	9.4	0.68	20	0.2	3	N	124	83	18	1.6
13	SS	83	9	11	2	0.69	20	1.4	0.1	100	73	4	0.7	11	6.9	0.74	30	0.1	2	N	130	83	3	0.8
14	MR	87	8	13	3.5	0.62	20	1.5	0.2	140	70	10	1.5	11	3.5	0.76	25	0.3	2	0.02	150	73	12	1.4
15	KS	50	7	6	2.3	0.75	15	1.3	0.25	130	6	12	1.5	8	2.3	0.73	40	0.3	3	N	128	66	10	1.5
16	RK	77	10	13	8.8	0.71	15	1.4	0.3	150	67	16	1.4	16	3.7	0.78	50	0.3	5	N	150	97	14	1.2
17	JS	70	9	10	5.4	0.72	15	1.6	0.1	143	67	8	1.5	10	3.9	0.74	25	0.2	2	N	132	66	9	1.5
18	SD	69	8	12	5.8	0.7	20	1.5	0.2	140	67	8	1.5	10	5.8	0.73	25	0.3	3	N	133	67	10	1.5
19	SK	66	8	11	6.3	0.75	N	1.5	0.2	133	79	8	1.6	11	6.2	0.74	N	0.2	2	N	126	76	11	1.7
20	CS	73	8	4	4.2	0.64	25	1.4	0.2	142	66	9	1.3	14	9.2	0.65	25	0.2	3	N	132	69	8	1.3
21	PCG	73	8	10	6.5	0.73	45	1.5	0.25	110	83	8	1.2	10	6.5	0.58	50	0.3	3	N	126	80	10	1.4
22	RK	73	9	12	4	0.76	5	1.3	0.2	158	83	10	1.6	6	3.8	0.78	25	0.3	2	0.02	142	81	12	1.5
23	GK	63	11	8	5.8	0.76	5	1.5	0.3	140	77	12	1.6	8	5.8	0.66	30	0.3	3		128	70	14	1.8
24	AK	73	11	10	5.8	0.78	N	1.6	0.2	148	63	10	1.8	9	5.8	0.79	30	0.3	3	N	152	67	9	1.6
25	HD	73	8	8	4.9	0.7	10	1.5	0.15	136	77	6	1.5	12	5.2	0.69	40	0.1	2	N	140	87	9	1.4
26	KS	73	10	10	6.8	0.72	15	1.4	0.2	134	73	16	2	3	9.4	0.72	25	0.15	2	N	122	83	14	1.8
27	BS	77	11	6	8.6	0.71	20	1.6	0.25	136	77	14	1.8	6	6.9	0.71	30	0.2	3	N	126	86	13	1.6
28	KK	67	12	11	5.4	0.76	15	1.5	0.2	136	63	16	1.9	6	5.4	0.76	25	0.25	3	N	124	67	14	1.8
29	GS	50	7	6	2.3	0.75	25	1.3	0.25	130	6	12	1.5	8	2.3	0.73	40	0.3	3	N	128	66	10	1.5
30	MH	77	10	13	8.8	0.71	20	1.4	0.3	150	67	16	1.4	16	3.7	0.78	40	0.3	5	N	150	97	14	1.2
31	BR	70	9	10	5.4	0.72	15	1.6	0.1	143	67	8	1.5	10	3.9	0.74	20	0.2	2	N	132	66	9	1.5
32	PL	69	8	12	5.8	0.71	20	1.5	0.2	140	67	8	1.5	10	5.8	0.74	25	0.3	3	N	133	67	10	1.5
33	BR	67	9	11	6.3	0.75	15	1.5	0.2	133	79	8	1.6	11	6.2	0.74	30	0.2	2	N	126	76	11	1.7
34	NS	73	11	5	4.2	0.64	30	1.4	0.2	141	66	9	1.3	14	9.2	0.65	35	0.2	3	N	132	69	8	1.3
35	GS	72	8	10	6.5	0.73	40	1.5	0.25	118	83	8	1.2	10	6.5	0.58	50	0.3	3	N	126	80	10	1.4
36	SS	73	9	12	4.8	0.76	15	1.4	0.2	156	83	10	1.6	6	3.8	0.78	30	0.3	2	0.02	142	81	12	1.5
37	VG	66	11	8	5.8	0.76	10	1.5	0.3	143	77	12	1.6	8	5.8	0.66	30	0.3	3		128	70	14	1.8
38	SG	72	11	10	5.8	0.78	N	1.7	0.2	148	63	10	1.8	9	5.8	0.79	25	0.3	3	N	152	67	9	1.6
39	LS	73	8	8	4.9	0.7	20	1.5	0.15	136	77	6	1.5	12	5.2	0.69	50	0.1	2	N	140	87	9	1.4
40	AG	74	10	10	6.8	0.72	30	1.5	0.2	134	73	16	2	3	9.4	0.72	25	0.15	2	N	122	83	14	1.8
41	NK	77	11	6	8.5	0.71	30	1.6	0.25	136	77	14	1.8	6	6.9	0.71	25	0.2	3	N	126	86	13	1.6
42	M	67	12	11	5.4	0.76	N	1.5	0.2	141	63	16	1.9	6	5.4	0.76	N	0.25	3	N	124	67	14	1.8
43	BK	63	9	11	9.2	0.73	N	1.2	0.3	142	70	9	1.7	8	9.2	0.73	25	0.3	2	0.04	138	73	10	1.6
44	RK	77	10	8	8.6	0.71	25	1.8	0.25	138	77	11	1.7	7	8.6	0.71	50	0.3	3	N	129	79	14	1.9
45	KS	73	9	12	4.8	0.7	20	1.6	0.2	138	73	10	1.5	14	3.8	0.78	25	0.2	3	N	126	70	12	1.6
46	AM	67	12	10	5.4	0.68	40	1.6	0.25	130	83	13	1.7	14	6.8	0.71	40	0.2	3	N	126	84	10	1.6
47	RS	73	10	10	6.8	0.67	25	1.5	0.25	148	67	13	1.5	8	6.8	0.68	30	0.25	3	N	136	67	12	1.4
48	AS	80	12	8	4.2	0.75	35	1.6	0.2	116	80	14	1.6	10	7.9	0.76	25	0.25	2	N	112	83	12	1.5
49	LR	67	12	12	7.8	0.74	40	1.8	0.1	130	80	14	1.2	12	7.8	0.75	50	0.1	3	N	128	93	12	1.5
50	M	83	10	9	3	0.69	30	1.8	0.25	148	77	16	1.8	6	3.2	0.69	25	0.3	3	N	142	80	14	1.6

						6-HR START OF IONOTROPE										12-HR OF START OF IONOTROPE						
S.No.	NAME	PPV	S.LACTATE	RRI	U.O	DOSE OF NOREPINEPHRINE	DOSE OF DOBUTAMINE	DOSE OF VASOPRESSIN	HR	BP	CVP	IVC	PPV	S.LACTATE	RRI	U.O	DOSE OF NOREPINEPHRINE	DOSE OF DOBUTAMINE	DOSE OF VASOPRESSIN	HR	MAP	CVP	IVC
1	KD	1.4	3.4	0.72	25	0.3	3	0.02	134	85	9	1.5	10	3.6	0.7	25	0.3	3	N	126	86	10	1.7
2	HD	13	7.6	0.77	50	0.1	2	N	124	83	10	1.2	12	5.4	0.71	75	0.15	2	N	113	82	11	1.5
3	NK	10	3.1	0.72	30	0.3	3	0.04	139	77	11	1.9	7	4.2	0.68	N	0.3	3	N	136	87	11	1.8
4	MS	10	8.6	0.77	30	0.3	2	0.02	146	83	10	1.7	9	8.2	0.71	50	0.3	2	0.02	130	85	9	1.5
5	SK	4	7.9	0.72	25	0.3	2	N	141	83	12	1.6	9	8.2	0.74	25	0.3	2	0.02	134	86	11	1.5
6	RL	13	2.4	0.72	25	0.2	3	N	116	77	11	1.4	12	2.1	0.71	60	0.15	2	N	112	87	10	1.5
7	KK	12	5.4	0.7	50	0.2	3	N	132	71	14	1.4	11	6.1	0.69	75	0.15	3	N	121	90	12	1.6
8	AS	9	5.2	0.72	20	0.3	2	0.02	142	77	12	1.3	11	4.8	0.79	25	0.3	2	0.01	128	80	11	1.4
9	BS	13	5.6	0.71	50	0.2	3	N	110	83	10	1.4	14	4.5	0.68	50	0.15	3	N	120	83	11	1.5
10	JG	10	3.8	0.65	75	0.2	2	N	133	83	16	1.8	9	2.4	0.53	60	0.1	1	N	114	90	15	1.8
11	TC	5	2.6	0.74	25	0.3	2	N	136	87	10	1.4	7	2.8	0.72	50	0.3	2	N	122	83	9	1.5
12	KK	3	9.4	0.78	30	0.05	3	N	116	89	20	1.8	2	9.7	0.5	50	0.2	3	0.02	112	83	13	1.8
13	SS	18	6.5	0.72	50	0.1	2	N	130	83	8	1.5	6	6.1	0.68	40	0.1	2	N	130	83	11	1.2
14	MR	15	3.5	0.61	30	0.3	3	0.03	140	83	6	1.5	12	3.2	0.58	30	0.3	3	N	150	87	10	1
15	KS	6	3.9	0.73	30	0.2	3	N	116	72	8	1.8	6	4.4	0.6	75	0.15	2	N	112	78	6	1.6
16	RK	4	6.9	0.68	50	0.3	3	N	146	89	12	1.3	10	7.3	0.66	70	0.3	2	N	146	88	12	1.2
17	JS	9	2.4	0.72	30	0.2	2	N	127	83	10	1.6	8	2.1	0.71	30	0.2	3	N	123	88	10	1.6
18	SD	8	6.3	0.74	30	0.2	3	N	126	82	12	1.6	8	5.4	0.71	30	0.15	2	N	128	84	10	1.6
19	SK	9	5.4	0.74	N	0.2	2	N	132	81	11	1.5	7	4.6	0.72	N	0.15	2	N	125	85	11	1.6
20	CS	12	11.1	0.62	60	0.15	2	N	118	71	8	1.4	12	6.6	0.6	70	0.15	2	N	110	72	6	1.4
21	PCG	10	6	0.62	70	0.25	2	N	110	77	8	1.4	11	6.5	0.55	75	0.2	2	N	100	77	7	1.5
22	RK	6	4.2	0.77	25	0.3	2	N	138	80	10	1.5	7	3.9	0.79	30	0.3	2	N	132	83	9	1.4
23	GK	7	5.4	0.74	30	0.25	3	N	127	80	10	1.8	6	4.6	0.71	30	0.25	3	N	116	90	10	1.6
24	AK	11	4.6	0.76	15	0.3	2	0.03	149	77	8	1.5	12	4.9	0.76	20	0.3	2	0.02	122	77	10	1.6
25	HD	10	4.9	0.7	50	0.15	2	N	145	79	10	1.6	10	3.9	0.7	35	0.1	2	N	136	83	9	1.6
26	KS	4	9.6	0.76	30	0.15	2	N	116	87	13	1.6	6	9.7	0.78	30	0.1	2	N	118	83	12	1.6
27	BS	8	6.3	0.76	40	0.15	2	N	114	86	12	1.5	9	6.1	0.73	50	0.15	2	N	111	89	11	1.4
28	KK	6	3.2	0.71	50	0.25	2	N	128	70	14	1.6	7	2.6	0.7	60	0.2	2	N	118	67	11	1.5
29	GS	6	3.9	0.73	30	0.2	3	N	116	72	8	1.8	6	4.4	0.6	75	0.15	2	N	112	78	6	1.6
30	MH	4	6.9	0.68	60	0.3	3	N	146	89	12	1.3	10	7.3	0.66	60	0.3	2	N	146	88	12	1.2
31	BR	9	2.4	0.72	25	0.2	2	N	127	83	10	1.6	8	2.1	0.71	30	0.2	3	N	123	89	10	1.6
32	PL	8	6.3	0.74	30	0.2	3	N	126	82	12	1.6	8	5.4	0.71	25	0.15	2	N	128	87	10	1.6
33	BR	9	5.4	0.74	25	0.2	2	N	132	81	11	1.5	7	4.6	0.72	30	0.15	2	N	125	85	11	1.6
34	NS	12	11.1	0.62	70	0.15	2	N	118	71	8	1.4	12	6.6	0.6	75	0.15	2	N	110	72	6	1.4
35	GS	10	6	0.62	70	0.25	2	N	110	77	8	1.4	11	6.5	0.55	75	0.2	2	N	100	77	7	1.5
36	SS	6	4.2	0.77	25	0.3	2	N	138	80	10	1.5	7	4.8	0.8	30	0.3	2	N	132	83	9	1.4
37	VG	7	5.4	0.74	25	0.25	3	N	127	80	10	1.8	6	4.6	0.71	30	0.25	3	N	116	90	10	1.6
38	SG	11	4.6	0.76	20	0.3	2	0.03	149	77	8	1.5	12	4.9	0.76	25	0.3	2	0.02	122	77	10	1.6
39	LS	10	4.9	0.7	40	0.15	2	N	145	79	10	1.6	10	3.9	0.7	40	0.1	2	N	136	83	9	1.6
40	AG	4	9.6	0.76	25	0.15	2	N	116	87	13	1.6	6	9.7	0.78	25	0.1	2	N	118	83	12	1.6
41	NK	8	6.3	0.76	40	0.15	2	N	114	86	12	1.5	9	6.1	0.73	50	0.15	2	N	111	89	11	1.4
42	M	6	3.2	0.71	40	0.25	2	N	128	73	13	1.6	7	2.6	0.71	50	0.2	2	N	118	71	11	1.5
43	BK	10	8.6	0.77	25	0.3	2	0.02	146	83	10	1.7	9	8.2	0.71	50	0.3	2	0.02	130	85	9	1.5
44	RK	4	7.9	0.72	30	0.3	2	N	141	83	12	1.6	9	8.2	0.74	30	0.3	2	0.02	134	86	11	1.5
45	KS	13	2.4	0.72	30	0.2	3	N	116	77	11	1.4	12	2.1	0.71	50	0.15	2	N	112	87	10	1.5
46	AM	12	5.4	0.7	50	0.2	3	N	132	71	14	1.4	11	6.1	0.69	60	0.15	3	N	121	90	12	1.6
47	RS	9	5.2	0.72	30	0.3	2	0.02	142	77	12	1.3	11	4.8	0.79	30	0.3	2	0.01	128	80	11	1.4
48	AS	13	5.6	0.71	50	0.2	3	N	110	83	10	1.4	14	4.5	0.68	50	0.15	3	N	120	83	11	1.5
49	LR	10	3.8	0.71	50	0.2	2	N	133	83	16	1.8	9	2.4	0.66	75	0.1	1	N	114	90	15	1.8
50	M	5	2.6	0.74	30	0.3	2	N	136	87	10	1.4	7	2.8	0.72	40	0.3	2	N	122	83	9	1.5

						24-HR OF STARTOF IONOTROPE										48-HRS OF START OF IONOTROPE							
S.No.	NAME	PPV	S.LACTATE	RRI	U.O	DOSE OF NOR EPINEPHRINE	DOSE OF DOBUTAMINE	DOSE OF VASOPRESSIN	HR	BP	CVP	IVC	PPV	S.LACTATE	RRI	U.O	DOSE OF NOREPINEPHRINE	DOSE OF DOBUTAMINE	HR	BP	CVP	IVC	PPV	S.LACTATE
1	KD	13	2.9	0.69	40	0.2	3	N	116	87	8	1.6	12	2.4	0.66	60	0.2	3	108	95	9	1.4	10	1.9
2	HD	10	3.2	0.66	75	0.1	1	N	106	87	9	1.3	12	2.1	0.62	75	N	1	94	88	10	1.5	11	0.9
3	NK	9	2.9	0.69	N	0.15	3	N	128	89	10	1.6	11	2.6	0.66	60	0.1	2	121	89	10	1.5	13	1.1
4	MS	12	7.2	0.7	35	0.3	2	0.01	130	85	9	1.5	12	7.2	0.7	50	0.25	2	116	97	7	1.5	12	6.4
5	SK	11	7.1	0.69	60	0.25	2	N	118	82	10	1.4	10	5.8	0.7	50	0.15	2	106	87	11	1.6	8	4.1
6	RL	13	1.9	0.71	60	0.15	2	N	108	89	9	1.5	10	1.6	0.68	65	0.1	2	110	90	10	1.6	11	1.1
7	KK	9	5.9	0.66	100	0.1	2	N	116	83	10	1.5	10	4.6	0.68	50	0.05	1	102	92	10	1.6	10	2.2
8	AS	10	4.6	0.73	50	0.25	2	N	132	77	12	1.4	9	5	0.69	50	0.15	2	119	87	10	1.5	8	3.2
9	BS	13	4.1	0.66	75	0.15	2	N	108	87	10	1.3	13	3.2	0.65	75	N	1	96	97	9	1.6	12	1.2
10	JG	9	4	0.52	100	N	2	N	112	77	13	1.7	12	2.5	0.55	100	N	2	114	84	10	1.8	10	1.1
11	TC	6	2.2	0.69	60	0.3	2	N	122	90	9	1.5	7	1.6	0.66	75	0.3	2	118	92	10	1.3	9	1.9
12	KK	6	6.4	0.55	75	0.2	3	N	113	80	12	1.7	4	4.5	0.55	80	0.2	2	106	83	10	1.9	2	2.3
13	SS	4	7.1	0.52	75	0.05	2	N	120	87	10	1.2	9	3.9	0.5	100	N	2	110	97	11	1.5	5	3.6
14	MR	19	4.1	0.5	60	0.1	3	N	130	90	7	1.5	9	1.5	0.53	75	0.3	3	140	90	10	1.7	8	3
15	KS	6	3.3	0.5	70	0.15	2	N	106	80	6	1.2	2	3.1	0.56	75	0.2	2	108	85	6	14	4	2
16	RK	11	6.2	0.64	60	0.3	2	N	144	87	10	1.3	9	5.1	0.64	60	0.3	2	141	90	8	1.2	8	4.3
17	JS	7	2.4	0.68	50	0.2	3	N	123	86	8	15	8	2.6	0.64	40	0.2	3	114	89	9	1.5	11	2.9
18	SD	7	4.5	0.69	50	0.15	2	N	120	85	8	1.4	6	3.8	0.63	60	0.2	2	114	85	10	1.5	9	4.1
19	SK	8	3.8	0.71	N	0.15	2	N	121	86	9	1.7	7	3.4	0.7	40	0.1	2	108	86	11	1.7	5	2.8
20	CS	11	4.4	0.58	75	0.15	2	N	118	69	9	1.6	11	2.1	0.55	75	0.1	2	102	68	6	1.3	12	2.4
21	PCG	11	4.8	0.54	75	0.2	2	N	98	87	9	1.5	12	3.2	0.51	75	0.1	1	118	83	10	1.5	14	4.3
22	RK	5	3	0.74	40	0.25	2	N	116	85	9	1.4	6	2.6	0.69	60	0.2	2	109	95	8	1.3	8	2.4
23	GK	10	4.3	0.65	60	0.2	3	N	108	83	8	1.5	10	4.1	0.62	70	0.15	2	104	90	8	1.5	11	3.6
24	AK	10	4.2	0.7	50	0.3	2	N	122	77	10	1.6	10	4.2	0.7	60	0.3	3	116	87	11	1.7	12	3.6
25	HD	10	3.8	0.68	60	0.1	2	N	126	80	6	1.4	13	3.6	0.66	60	0.1	2	112	83	10	1.6	7	2.8
26	KS	8	6.3	0.69	40	0.15	2	N	122	84	10	1.5	10	4.2	0.66	75	0.1	2	112	91	9	1.5	10	2.3
27	BS	9	7.1	0.7	50	0.15	2	N	114	86	10	1.5	10	4.2	0.68	70	0.15	2	106	77	10	1.5	11	3.6
28	KK	8	2.2	0.68	50	0.15	2	N	116	81	11	1.6	9	1.9	0.65	70	N	2	104	87	12	1.5	10	0.9
29	GS	6	3.3	0.5	100	0.15	2	N	106	80	6	1.2	2	3.1	0.56	65	0.2	2	108	85	6	14	4	2
30	MH	11	6.2	0.64	60	0.3	2	N	144	87	10	1.3	9	5.1	0.64	60	0.3	2	141	90	8	1.2	8	4.3
31	BR	7	2.4	0.68	50	0.2	3	N	123	86	8	15	8	2.6	0.64	30	0.2	3	114	89	9	1.5	11	2.9
32	PL	7	4.6	0.69	30	0.15	2	N	120	85	8	1.4	6	3.8	0.63	60	0.2	2	114	85	10	1.5	9	3.2
33	BR	8	3.8	0.71	30	0.15	2	N	121	86	9	1.7	7	3.4	0.7	50	0.15	2	108	86	11	1.7	5	2.8
34	NS	11	4.4	0.58	75	0.15	2	N	118	69	9	1.6	11	2.1	0.55	75	0.1	2	102	68	6	1.3	12	2.4
35	GS	11	4.8	0.54	100	0.2	2	N	98	87	9	1.5	12	3.2	0.52	100	0.1	1	118	83	10	1.5	14	4.3
36	SS	5	4.1	0.73	50	0.25	2	N	116	85	9	1.4	6	3.8	0.69	60	0.2	2	109	95	8	1.3	8	3.1
37	VG	10	4.3	0.65	60	0.2	3	N	108	83	8	1.5	10	4.1	0.62	75	0.15	2	104	90	8	1.5	11	3.6
38	SG	10	4.2	0.7	50	0.3	2	N	122	77	10	1.6	10	4.2	0.7	60	0.3	3	116	87	11	1.7	12	2.6
39	LS	10	3.8	0.68	50	0.1	2	N	126	80	6	1.4	13	3.6	0.67	60	0.1	2	112	83	10	1.6	7	2.8
40	AG	8	6.3	0.69	30	0.15	2	N	122	84	10	1.5	10	4.2	0.66	60	0.1	2	112	91	9	1.4	10	2.3
41	NK	9	7.1	0.7	50	0.15	2	N	114	86	10	1.5	10	4.2	0.68	60	0.15	2	106	77	10	1.6	11	3.1
42	M	8	2.2	0.68	60	0.15	2	N	116	81	11	1.6	9	1.9	0.65	70	N	2	104	87	12	1.5	10	0.9
43	BK	12	7.2	0.7	35	0.3	2	0.01	130	85	9	1.5	12	7.2	0.7	50	0.25	2	116	97	7	1.5	12	6.4
44	RK	11	7.1	0.69	60	0.25	2	N	118	82	10	1.4	10	5.8	0.7	50	0.15	2	106	87	11	1.6	8	4.1
45	KS	13	1.9	0.71	50	0.15	2	N	108	89	9	1.5	10	1.6	0.68	60	0.1	2	110	90	10	1.6	11	1.1
46	AM	9	5.9	0.66	75	0.1	2	N	116	83	10	1.5	10	4.6	0.68	60	0.05	1	102	92	10	1.6	10	2.2
47	RS	10	4.6	0.73	40	0.25	2	N	132	77	12	1.4	9	5	0.69	60	0.15	2	119	87	10	1.5	8	3.2
48	AS	13	4.1	0.69	50	0.15	2	N	108	87	10	1.3	13	3.2	0.65	70	N	1	96	97	9	1.6	12	1.2
49	LR	9	4	0.58	75	N	2	N	112	77	13	1.7	12	2.5	0.55	100	N	2	114	84	10	1.8	10	1.1
50	M	6	2.2	0.69	50	0.3	2	N	122	90	9	1.5	7	1.6	0.66	60	0.3	2	118	92	10	1.3	9	1.9

S.No.	NAME	RRI	U.O	HB			TLC			S.UREA			AKI	S.CREATININE			SODIUM			POTASSIUM			CHLORIDE			SOFA SCORE			EJECTION FRACTION			MECHANICAL VENTILATION	28-D MORTALITY
				D1	D2	D3	D1	D2	D3	D1	D2	D3		D1	D2	D3	D1	D2	D3	D1	D2	D3	D1	D2	D3	D1	D2	D3	D1	D2	D3		
1	KD	0.62	70	15.2	13.6	12.9	11.2	14.8	12.6	64	71	82	1	1.2	1.6	1.45	142	143	148	4.1	3.7	3.9	103	110	110	11	9	9	35	32	32	Y	Y
2	HD	0.59	80	8.9	10.1	9.4	14.1	12.9	10.6	21	24	22	1	1.32	1.68	1.49	144	145	142	3.9	3.4	3.5	104	106	108	6	4	3	60	60	60	Y	N
3	NK	0.67	50	14.1	13.8	13.9	11.2	13.6	10.1	69	76	84	2	1.64	1.72	1.51	143	145	148	4.3	3.9	3.4	114	112	111	9	6	8	60	60	60	N	N
4	MS	0.64	60	12.2	13.7	12.6	14.2	13.1	18.6	21	29	34	2	0.77	1.2	1.4	137	143	143	4.1	3.6	3.2	102	107	106	9	6	4	60	60	60	Y	N
5	SK	0.66	50	9.2	8.9	8.8	12.9	14.4	16.3	20	24	28	1	1.2	1.6	1.5	145	145	143	3.7	2.9	3.4	110	106	108	10	6	4	60	60	60	Y	N
6	RL	0.64	60	11.8	12.1	11.6	17.2	14.6	16.8	19	28	21	1	1.27	1.64	1.49	143	14	144	3.9	3.2	3.6	108	108	109	9	6	5	60	60	60	Y	N
7	KK	0.64	60	8.6	7.6	8.9	16.2	18.4	14.2	82	112	118	3	2.9	3.1	3.6	134	139	145	4.2	4.6	4.1	99	103	110	10	6	6	28	30	32	N	N
8	AS	0.64	70	12.1	11.6	11.4	16.8	22.4	20.9	29	32	41	1	0.62	0.91	1.1	138	143	148	4.1	3.9	3.82	101	106	110	11	10	8	60	60	60	Y	N
9	BS	0.66	60	10.9	11	9.6	5.6	7.8	7.2	25	22	28	N	0.67	0.78	0.66	138	139	144	4.6	4.1	3.8	105	102	104	9	7	6	25	28	28	Y	N
10	JG	0.45	100	8.3	7.4	8.5	16.6	22.1	19.5	89	112	140	3	3.88	3.91	4.34	128	132	138	4.9	5.2	4.6	93	98	102	7	5	5	30	32	32	Y	N
11	TC	0.64	60	14.2	10.6	9.3	11.8	12.6	9.2	34	41	38	1	0.62	0.66	0.58	143	143	148	3.9	4.2	4.6	108	106	109	11	9	8	32	26	30	N	N
12	KK	0.5	100	8.9	7.7	7.4	12.9	7.1	8.8	19	22	18	1	1.47	1.61	1.48	145	145	144	3.76	2.98	3.12	111	107	106	9	7	6	60	60	60	Y	Y
13	SS	0.5	100	11.4	10.7	9.9	3.8	3.5	5.5	25	55	53	N	0.59	0.98	0.81	136	139	144	4.91	4.26	4.06	105	108	109	3	2	1	60	60	60	Y	Y
14	MR	0.6	75	15.1	13.8	12.6	7.2	8.5	3	69	75	88	1	1.64	1.74	1.46	142	146	150	4.1	3.69	3.63	113	117	119	9	8	10	60	60	60	Y	Y
15	KS	0.54	100	10.4	10.2	10	9.9	6.6	8.4	25	30	48	N	0.48	0.6	0.7	145	142	148	3.85	3.85	3.9	109	112	114	9	6	6	20	23	22	N	N
16	RK	0.66	60	14.2	5.7	14.9	28.2	32.2	33	21	29	24	N	0.67	1.1	0.9	137	145	138	4.09	3.9	4.1	104	108	103	14	11	10	16	20	20	Y	Y
17	JS	0.62	75	10.4	9.5	9.1	40.5	29	39.8	65	68	69	3	1.94	2.4	2.48	130	135	138	3.4	3.86	4.1	100	102	103	8	7	5	60	60	60	Y	Y
18	SD	0.64	70	9.8	9.6	9.6	20.1	18.2	24.1	67	48	52	2	1.63	1.4	1.38	146	145	146	4.8	4.6	4.2	106	108	106	9	7	6	40	40	38	Y	Y
19	SK	0.66	60	10.2	10.8	10.5	21	19.6	18.5	54	48	38	3	1.92	2.1	2.06	148	145	144	4.1	5.1	4.6	109	111	108	9	6	6	60	60	60	Y	Y
20	CS	0.48	100	10	9.8	9.4	24	18	20	64	68	42	N	0.9	1.1	0.9	140	139	142	3.9	3.8	3.6	110	106	102	9	6	4	60	60	60	Y	N
21	PCG	0.53	80	11.6	11.4	10.8	14	18	11	110	116	60	1	1.8	1.4	1.6	140	136	143	3.8	4.1	3.6	114	110	110	14	12	11	60	60	60	Y	N
22	RK	0.66	75	15.2	13.6	12.9	7.3	8.9	10.2	70	68	60	1	1.43	1.62	1.31	142	143	150	4.1	3.9	3.9	112	108	118	11	9	8	60	60	60	Y	N
23	GK	0.58	100	10.8	10.2	10.1	26.2	20.1	18.6	25	30	48	N	0.48	0.56	0.72	143	142	145	3.8	3.6	4.1	103	109	108	10	8	7	25	28	26	Y	N
24	AK	0.62	70	14.1	13.8	13.6	11.6	7.2	5	72	75	68	1	1.54	1.76	1.45	144	146	148	4.2	4.1	4	113	108	106	11	9	8	60	60	60	N	N
25	HD	0.63	70	12.9	12.4	12.1	3.7	3.8	5	6	11	9	N	0.62	0.73	0.69	145	143	140	3.4	3.7	3.9	116	112	108	10	9	9	60	60	60	Y	Y
26	KS	0.62	60	9	8.8	8.6	12.9	8.9	7.6	19	24	19	2	1.62	1.56	1.76	145	146	144	3.8	3.9	3.6	104	103	106	14	12	11	60	60	60	Y	Y
27	BS	0.6	70	11.6	10.8	9.6	3.1	2.8	5.2	25	50	48	N	0.6	0.9	0.81	136	139	140	4.8	4.2	4.1	105	106	108	11	9	10	60	60	60	Y	N
28	KK	0.59	75	9.3	8.9	8.8	16.2	21.6	19.6	86	100	110	3	3.2	3.9	4.2	136	140	139	4.6	4.2	4.3	98	102	104	10	7	6	30	32	32	Y	Y
29	GS	0.54	100	10.4	10.2	10	9.9	6.6	8.4	25	30	48	N	0.48	0.6	0.69	145	142	148	3.85	3.85	3.9	109	112	114	9	6	6	20	23	22	N	N
30	MH	0.63	75	14.2	5.7	14.9	28.2	32.2	33	21	29	24	N	0.67	1.1	0.9	137	145	138	4.09	3.9	4.1	104	108	103	14	11	10	16	20	20	Y	Y
31	BR	0.62	30	10.4	9.5	9.1	40.5	29	39.8	65	68	69	3	1.94	2.4	2.38	130	135	138	3.4	3.86	4.1	100	102	103	8	7	5	60	60	60	Y	N
32	PL	0.59	100	9.8	9.6	9.6	20.1	18.2	24.1	67	48	52	1	1.63	1.4	1.38	146	145	147	4.6	4.6	4.2	106	108	106	9	7	6	40	40	38	Y	N
33	BR	0.64	60	10.2	10.8	10.5	21	19.6	18.5	54	48	38	2	1.9	2.1	2.08	148	145	144	4.1	5.1	4.6	109	111	108	9	6	6	60	60	60	Y	Y
34	NS	0.48	100	10	9.8	9.4	24	18	20	64	68	42	1	0.9	1.1	0.98	140	139	142	3.9	3.8	3.5	111	106	102	9	6	4	60	60	60	N	N
35	GS	0.53	80	11.6	11.4	10.8	14	18	11	110	116	60	1	1.8	1.4	1.6	140	136	143	3.8	4.1	3.6	114	110	110	14	12	11	60	60	60	Y	N
36	SS	0.66	60	15.2	13.6	12.9	7.3	8.9	10.2	70	68	60	1	1.43	1.6	1.42	142	143	150	4.1	3.9	3.9	112	108	118	11	9	8	60	60	60	Y	Y
37	VG	0.58	75	10.8	10.2	10.1	26.2	20.1	18.6	25	30	48	N	0.48	0.56	0.72	143	142	146	3.8	3.6	4.1	103	109	108	10	8	7	25	28	26	Y	Y
38	SG	0.62	60	14.1	13.8	13.6	11.6	7.2	5	72	75	68	1	1.54	1.76	1.79	140	142	148	4.2	4.1	4	109	108	106	11	9	8	60	60	60	N	N
39	LS	0.63	60	12.9	12.4	12.1	3.7	3.8	5	6	11	9	N	0.62	0.73	0.69	145	143	142	3.5	3.7	3.9	116	106	102	10	7	6	60	60	60	N	N
40	AG	0.62	70	9	8.8	8.6	12.9	8.9	7.6	19	24	19	2	1.62	1.56	1.76	145	146	144	3.8	3.9	3.6	104	103	106	14	12	11	60	60	60	Y	N
41	NK	0.6	70	11.6	10.8	9.6	3.1	2.8	5.2	25	50	48	N	0.6	0.9	0.81	136	139	140	4.7	4.2	4.1	105	106	108	11	9	10	60	60	60	Y	Y
42	M	0.59	80	9.3	8.9	8.8	16.2	21.6	19.6	86	100	110	3	3.2	3.9	3.9	136	140	139	4.6	4.2	4.3	98	102	104	10	7	6	30	32	32	N	N
43	BK	0.64	70	12.2	13.7	12.6	14.2	13.1	18.6	21	29	34	2	0.77	1.2	1.4	137	143	143	4.1	3.6	3.2	102	107	106	9	6	4	60	60	60	Y	N
44	RK	0.66	60	9.2	8.9	8.8	12.9	14.4	16.3	20	24	28	1	1.2	1.6	1.5	145	145	143	3.7	2.9	3.4	110	106	108	10	6	4	60	60	60	Y	Y
45	KS	0.64	75	11.8	12.1	11.6	17.2	14.6	16.8	19	28	21	1	1.27	1.64	1.49	143	14	144	3.9	3.2	3.6	108	108	109	9	6	5	60	60	60	N	N
46	AM	0.64	70	8.6	7.6	8.9	16.2	18.4	14.2	82	112	118	3	2.9	3.1	3.6	134	139	145	4.2	4.6	4.1	99	103	110	10	6	6	28	30	32	Y	N
47	RS	0.64	70	12.1	11.6	11.4	16.8	22.4	20.9	29	32	41	N	0.62	0.91	1.1	138	143	148	4.1	3.9	3.82	101	106	110	11	10	8	60	60	60	Y	N
48	AS	0.66	60	10.9	11	9.6	5.6	7.8	7.2	25	22	28	N	0.67	0.78	0.66	138	139	144	4.6	4.1	3.8	105	102	104	9	7	6	25	28	28	Y	N
49	LR	0.58	100	8.3	7.4	8.5	16.6	22.1	19.5	89	112	140	3	3.88	3.91	4.34	128	132	138	4.9	5.2	4.6	93	98	102	7	5	5	30	32	32	N	N
50	M	0.64	60	14.2	10.6	9.3	11.8	12.6	9.2	34	41	38	N	0.62	0.66	0.58	143	143	148	3.9	4.2	4.6	108	106	109	11	9	8	32	26	30	Y	N

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Subject: Approval of Plan of Thesis.

This is to inform you that the Faculty of Medical Sciences in its meeting held on 22.01.2021 has approved the plan of thesis of Dr Mandava Venkata Sravani, a student of your college for DM Critical Care Medicine along with the names of Supervisor/Co-Supervisor as under:-

Topic Plan of Thesis
Effect of dobutamine on renal resistive index in septic shock patients

Supervisor
Dr. Gunchan Paul
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Co-Supervisor
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The student has to submit the three copies of thesis (along with PDF format) , to the Controller of Examinations, BFUHS, Faridkot, at least six months before the commencement of theory examination, if he/she is otherwise eligible to take the examination. He /She must directed to attach a photocopy of this letter with the forwarding letter while submitting thesis to the University along with the letter of approval of University for change of supervisor/Co-Supervisor, change of topic,(if any).

Dr. S P Singh MS(Oph)
Controller of Examinations

Note :
5. *If any discrepancy found regarding topic of thesis or Supervisor/Co-Supervisor, inform undersigned within one month after issue of this letter.*

EFFECT OF DOBUTAMINE ON RENAL RESISTIVE INDEX IN SEPTIC SHOCK PATIENTS

THESIS PROPOSAL

FOR APPROVAL OF SUBJECT OF THESIS TO BE SUBMITTED

IN PARTIAL FULFILMENT OF THE REQUIREMENTS

FOR THE DEGREE OF

DOCTORATE OF MEDICINE

IN

CRITICAL CARE MEDICINE

OF THE

BABA FARID UNIVERSITY OF HEALTH SCIENCES
FARIDKOT

MARCH, 2020

DR. MANDAVA VENKATA SRAVANI

DEPARTMENT OF CRITICAL CARE MEDICINE
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ABSTRACT OF PLAN OF THESIS

Title	EFFECT OF DOBUTAMINE ON RENAL RESISTIVE INDEX IN SEPTIC SHOCK PATIENTS
For the degree of	D.M. Critical Care Medicine
Name of the candidate	Dr. Mandava Venkata Sravani
Supervisor	Dr. Gunchan Paul, Associate Professor, Department of Critical Care Medicine, DMCH, Ludhiana
Co-supervisor	Dr. Parshotam Lal Gautam, Professor & Head, Department of Critical Care Medicine, DMCH, Ludhiana
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Introduction: Septic shock is defined as "subset of sepsis with circulatory and cellular/metabolic dysfunction associated with higher risk of mortality." After appropriate resuscitation if MAP does not improve to about 65 mm Hg it is recommended that vasopressors be initiated. Norepinephrine is recommended as the initial vasopressor as per Surviving Sepsis campaign recommendations. It is recommended to use second vasopressor to reduce the dose of first considering side effects of high dose of norepinephrine. Second choice is always so far based on clinical judgement and arbitrary between epinephrine, vasopressin and dobutamine. However none of the above vasopressors were proven to be strongly beneficial after Nor-Epinephrine and no definitive strong recommendations were made regarding the second choice of vasopressor. Renal Resistive Index (RRI) is a sonographic measurement of resistance to flow in intrarenal arcuate or interlobar arteries. An inverse relationship between MAP and RRI has been strongly demonstrated.

Aim of Study: To evaluate the effect of dobutamine on Renal Resistive Index in septic shock patients.

Materials & Methods: Patients with septic shock will initially be resuscitated with crystalloids to maintain a MAP ≥65 mm Hg. Following adequate resuscitation, if the MAP still remains less than 65 mm Hg then nor- epinephrine will be used as the first line vasopressor.2 Once MAP > 65 mm Hg, dobutamine infusion is started at 3µg/kg/min. The response to these ionotropes and resuscitation will be monitored by vital parameters continuously and both lactate and RRI will be monitored periodically.

Clinical Significance: This study will guide vasopressor choice in septic shock patients by using RRI as a monitoring tool for organ perfusion.

Keywords: Septic shock, Renal Resistive Index, Vasopressor.

(Signature) Candidate	(Signature) Co-supervisor	(Signature) Supervisor	(Signature) Principal

CERTIFICATE OF FACILITIES AVAILABLE

This is to certify that the facilities for work on the subject of thesis titled **"EFFECT OF DOBUTAMINE ON RENAL RESISTIVE INDEX IN SEPTIC SHOCK PATIENTS"** exist in the Department of Critical Care Medicine, DMC&H, Ludhiana and will be provided to the candidate. We will see that the data being included in the thesis is genuine and is collected by the candidate herself under our supervision and guidance.

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6 BRIEF RESUME OF THE INTENDED WORK

6.1 NEED FOR THE STUDY

Sepsis is a clinical syndrome caused by host's response to infection and has got profound adverse physiological effects. Sepsis is believed to be one the leading cause of in-hospital mortality and morbidity in recent times. 1 The Third International Consensus Definitions of Sepsis and Septic Shock guidelines (Sepsis-3) defines "Sepsis as a life threatening organ dysfunction caused by dysregulated host response to infection" and septic shock as "subset of sepsis with circulatory and cellular/metabolic dysfunction associated with higher risk of mortality."[1,2,3]

Owing to the ambiguity and complexity of sepsis, it is extremely difficult to set concrete criteria for identifying it and forming definitive guidelines in the management of sepsis. However, there had always been emphasis on early initiation of resuscitation and treatment of sepsis. This lead to the most important revision of SSC bundle that the 3-hour and 6-hour bundles into a single "hour-1 bundle" in the SSC update 2018.[3,4]

SSC update 2018 recommends initiation of resuscitation and treatment, such as measuring lactate, obtaining blood cultures, administration of fluids and antibiotics and initiation of vasopressors to target MAP should be initiated within one hour. However, more than one hour may be required to complete resuscitation.[4]

The guidelines recommend rapid administration of crystalloid at 30ml/kg in case of hypotension or if lactate is ≥2 mmol/L.3,4 The American College of Critical Care Medicine (ACCM) recognize that a MAP of atleast 65 mm Hg is required to perfuse organs. If after appropriate resuscitation the MAP does not improve to about 65 mm Hg it is recommended that vasopressors be initiated.3,4 Norepinephrine is recommended as the initial vasopressor as per Surviving Sepsis campaign recommendations (Strong recommendation & low quality evidence). The next choice can either be vasopressin or epinephrine as per the guidelines (weak recommendation & low quality

evidence). Dobutamine is suggested in patients with evidence of persistent hypoperfusion despite adequate fluid resuscitation and use of other vasopressor agents (weak recommendation, low quality evidence). The end point of the resuscitation is ultimately determined by the organ perfusion and the vasopressor's dosage should be titrated accordingly.[2]

Serum lactate is being used as a surrogate marker of organ perfusion in sepsis.[2,3] However serum lactate cannot be considered as a direct measure of organ perfusion, as it can be raised in other causes such as liver failure.[2,5] This necessitates the need for alternative objective indicator of organ perfusion.[2,5] Patients with multiple co-morbid conditions including chronic illness (e.g., diabetes) and chronic organ dysfunction (e.g., liver or renal failure) and on catacholamine infusion can cause increase in lactate levels despite adequate organ perfusion.[2,5]

Acute kidney injury is an important early marker of organ perfusion. 6AKI is seen in 25% of sepsis patients in ICU.[6] Bedside ultrasound Doppler can be used as a non-invasive tool to assess the renal circulation.[6,7] Renal Resistive Index (RRI) is a sonographic measurement of resistance to flow in intrarenal arcuate or interlobar arteries. An inverse relationship between MAP and RRI has been strongly demonstrated, owing to the post-glomerular vasoconstriction during hypoperfusion to maintain GFR.[6] It was found that patients in shock have a higher RRI when compared to patients without shock.[8,9]

It is recommended to use second vasopressor to reduce the dose of first considering side effects of high dose of norepinephrine.[2] Second choice is always so far based on clinical judgement and arbitrary between epinephrine, vasopressin and dobutamine. Clinical judgement is mainly based on co-existance of co-morbidities such as IHD, heart rate, mean arterial pressure and haemodynamic response. However none of the above vasopressors were proven to be strongly beneficial after Nor-Epinephrine and no definitive strong recommendations were made regarding the second choice of vasopressor.[2] Owing to the lacunae in the second choice vasopressor,

this study aims at using Doppler RRI as a surrogate marker and early index of hypoperfusion and assist the choice of vasopressor in septic shock. The secondary aim is to assess the relationship of RRI to AKI and lactate in septic shock.

6.2 REVIEW OF LITERATURE

Sepsis is a life-threatening complication in response to infection causing end-stage organ dysfunction and death. The word sepsis is derived from greek term "σήψις" which means "make rotten" or "decomposition". The term was first described by Hippocrates in 400 BCE to describe the process through which infected wounds become purulent. Although the term sepsis dated old, it took over more than 2000 years to understand the pathophysiology of sepsis.[10] Despite advancements in the understanding of the clinical syndrome, hemodynamic monitoring devices and treatment modalities, sepsis is still one of the leading cause of mortality in ICU patients.[11]

Globally, more than 30 million people are affected by sepsis every year worldwide, with 6 million deaths occurring annually.[11] It is estimated to affect 1 to 1.5 million persons per year in USA causing more than 200,000 deaths every year.[12] As per SSC 2012 data, mortality rates due to sepsis are 41% in Europe compared to 28.3% in United States.[11]

Definitions:

Sepsis 3 (2016): "Sepsis is a life-threatening organ dysfuction caused by fysregulated host response to infection".[1,2]

Clinical criteria for sepsis: Suspected or documented infection and an acute increase of ≥2 SOFA points.[11]

The task force considered that positive qSOFA (quick SOFA) criteria should also prompt consideration of possible infection in patients not previously recognized as infected.[10,11]

qSOFA criteria:

Altered mental status (GCS score <15)

Systolic blood pressure <100 mm Hg

Respiratory rate >22 breaths per min

Septic shock is defined as " subset of sepsis in which underlying circulatory and cellular metabolism abnormalities are profound enough to substantially increase mortality.[1,2]

Septic shock can be identified with a clinical construct of sepsis with persisting hypotension, requiring vasopressor therapy to elevate MAP

≥65 mm Hg and lactate >2 mmol/L despite adequate fluid resuscitation.[1,2,12]

The paramount importance in the management of patients with sepsis and septic shock is that it is a medical emergency requiring assessment and management on urgent basis. This lead to the further modification of the SSC 2016 guidelines with an update in 2018. The elements of SSC bundle 2018 are given in Table 1[1]

Table 1: HOUR-1 BUNDLE
1. Measure lactate level. Remeasure if initial lactate is >2mmol/L
2. Obtain blood cultures prior to administration of antibiotics
3. Administer broad-spectrum antibiotics
4. Begin rapid administration of 30ml/kg crystalloid for hypotension or lactate ≥4 mmol/L
5. Apply vasopressors if patient is hypotensive during or after fluid resuscitation to maintain MAP ≥65 mm Hg.

Early effective resuscitation is crucial to prevent organ hypoperfusion in a patient with septic shock. Hence initial fluid resuscitation with 30ml/kg crystalloids should be initiated immediately upon recognizing patient with sepsis, elevated lactate and/or hypotension (strong recommendation, low quality evidence). Fluid administration beyond initial resuscitation needs careful reassessment as a sustained positive balance can be detrimental.[1,2] This reassessment includes physiological variables such as blood pressure, heart rate, urine output, noninvasive monitoring by PLR, PPI, IVC collapsibility index and invasive monitoring such as SPV, PPV, CVP. In

patients not responding to fluids, they are managed by vasoactive agents to maintain a MAP ≥65 mm Hg.[2]

Norepinephrine is the first choice vasopressor recommended (strong recommendation, moderate quality evidence).[2] Norepinephrine increases MAP due to its vasoconstrictive effects, with little changes in heart rate and more effective at reversing hypotension in patients with septic shock. However a high dose of norepinephrine can cause organ hypoperfusion, bowel ischemia, increase cellular energy expenditure, hyperglycemia.[13] Hence, SSC guidelines suggests adding either vasopressin (0.03U/min) (weak recommendation, moderate quality evidence) or epinephrine (weak recommendation, low quality of evidence) with an intent to decrease the decrease norepinephrine dosage. Dobutamine is suggested in patients with evidence of persistent hypoperfusion despite adequate fluid resuscitation and use of other vasopressor agents (weak recommendation, low quality evidence). The end point of the resuscitation is ultimately determined by the organ perfusion and the vasopressor's dosage should be titrated accordingly.[2]

Although vasopressor support reverses hypotension but it does not reflect organ perfusion. Serum lactate is used a surrogate marker of organ perfusion according to SSC guidelines. If the initial lactate is >2mmol/L, re measured within 2-4h to guide resuscitation to normalize lactate (Weak recommendation, low quality evidence).[1] However serum lactate is not a direct measure of organ perfusion. Serum lactate is increased in sepsis due to various other reasons such as hepatic failure, renal failure, myeloproliferative disease, pancreatitis, short bowel syndrome, hypoxia, anemia, regional ischemia and drugs such as catecholamines, biguanides, methanol, ethanol, ethylene glycol.[5] A single lactate measurement cannot guide in resuscitation and sequential measurements are required to guide treatment. Serum lactate measurement is an indirect nonspecific indicator of organ hypoperfusion, hence a more sensitive and specific indicators of organ hypoperfusion are needed to guide therapy.[2,5]

Septic shock is severe condition which organ hypoperfusion. Most commonly affected organ is kidney. AKI is seen in 25% of cases with sepsis and 50% of septic shock patients in ICU.[6] AKI increases morbidity and morbidity in septic shock patients if not addressed early in the course of disease. Underlying mechanism of AKI can be either organ hypoperfusion, cellular injury due to oxidative stress, drug toxicity.[8]

Many markers have been recognized to assess early predictors of AKI such as neutrophil gelatinase-associated lipocalin, tissue inhibitor of metalloprotease-2, kidney injury molecule-1 and insulin-like growth factor binding protein-7. However, none of these markers have shown any proven benefit in management of AKI patients. Instead they are not found to be cost-effective and are time taking.[14] Bedside ultrasound Doppler of renal vessels is a noninvasive, easily accessible, repeatable tool which gives a real time monitoring of renal persfusion.[8,14] The changes in RRI are noted earlier before the changes in S.creatinine during both development and recovery phase of AKI.[14]

RRI has good sensitivity and specificity in diagnosing AKI, even in patients on vasoactive agents. A RI >0.795 predicted AKI with 82% sensitivity and 92% specificity.[14] Renal Resistive Index (RRI) is a sonographic measurement of resistance to flow in intrarenal arcuate or interlobar arteries. Renal Resistive Index is calculated as (Vmax – Vmin)/ Vmax, where Vmax = peak systolic velocity and Vmin = minimal diastolic velocity.[15]

Rozemeijer et al., in his prospective observational study on renal resistive index in shock concluded that patients with shock had a higher RRI than patients without shock.[8]

Deruddre et al., in his study on renal resistive index in septic shock found that renal resistive index helps to determine the optimal MAP needed for renal blood flow to be maintained and to titrate the hemodynamic resuscitation in septic shock.[16]

Antal et al., in his study on hemodynamic predictors for sepsis on AKI concluded that severe vasoplegia in first 24hours as determined

by low SVR through the need of vasopressors to maintain a MAP ≥65 mm Hg in absence of hypovolemia was associated with higher risk of sepsis induced AKI.[17]

In septic shock, nor-epinephrine is the first choice of vasopressor according to SSC guidelines (strong recommendation, moderate quality evidence).[2] However, no strong recommendations have been made regarding the second choice of vasopressor after nor-epinephrine.[2] The patient outcome with the use of specific vasopressor is unpredictable. Hence the question of ideal ionotrope/vasopressor in patients with septic shock remains unanswered and controversial.[18]

Mahmoud et al., in his study on dobutamine vs epinephrine in patients with septic shock concluded that use of epinephrine was superior to dobutamine to maintain cardiovascular parameters but inferior to dobutamine when increase in serum lactate concentration and maintaining systemic pH were considered.[18]

Nadeem et al, in his meta-analysis on effect of dobutamine in septic shock patients found that cardiovascular parameters in the form of VO2, CI, DO2, RAP and O2 extraction improved with dobutamine in septic shock patients with no significant changes in HR, MAP,PaO2.[19]

Kasugai et al in his study on responsiveness to epinephrine in norepinephrine-refractory septic shock in 41 patients found that 59% responded to shock and a higher 28-day survival rate. A better hemodynamic status in refractory shock patients is observed with early administration of epinephrine in norepinephrine refractory shock.[20]

Present study focuses on the choice of second ionotrope in patients with septic shock who are refractory to fluid resuscitation and a low dose nor-epinephrine. There were no strong recommendations regarding second choice vasopressor. The effect of these ionotropes on hemodynamic parameters and organ perfusion needs to be established, as there were not many studies on it. Owing to this lacunae, our present study focuses on dobutamine in septic shock patients using renal resistive index as a monitoring tool to titrate the hemodynamic resuscitation and evaluate the organ perfusion.

6.3 AIMS AND OBJECTIVES OF THE STUDY

Primary objective:

To evaluate the affect of dobutamine on Renal Resistive Index in septic shock patients.

Secondary objective:

1. To assess the relationship of RRI with lactate in septic shock.
2. To assess the relationship of RRI with AKI in septic shock.

7.0 MATERIALS AND METHODS

7.1 SOURCE OF DATA

Study design: Prospective observational study

Study place: Intensive care units, Dayanand Medical College, Ludhiana

Study Period: March 2020 to March 2021

7.2 METHOD OF COLLECTION OF DATA

Inclusion criteria:

1. All patients admitted to ICU under Critical Care Medicine with septic shock.

Exclusion criteria:

1. Age less than 18 years or older than 65 years.
2. AKI on renal replacement therapy (RRT) or with an expectation of RRT within 24 hours.
3. Known case of renal artery stenosis, chronic kidney disease defined by a glomerular filtration rate of less than 30mL/min/1.73m2.
4. Cirrhosis with hepatorenal syndrome
5. Use of renin-angiotensin-aldosterone antagonists
6. Pregnancy

Definitions:

The Third International Consensus Definitions of Sepsis and Septic Shock (Sepsis-3)[1,2,11].

Sepsis: "Life threatening organ dysfunction caused by a dysregulated host response to infection." For the sake of clinical operationalization, organ dysfunction is represented by increase in SOFA score of ≥2 points, which is associated with an in-hospital mortality >10%.[1,2,11]

Clinically, any suspected case of infection with an increase in SOFA score of ≥2 points or at least 2 of the following signs:[1,2,11]

qSOFA: Respiratory rate ≥22/min

Altered mental status

Systolic blood pressure <100 mm Hg.

Septic shock: "Sepsis with circulatory and cellular/metabolic dysfunction", clinically described by a vasopressor requirement to

maintain a MAP ≥65 mm Hg and serum lactate > 2mmol/L in the absence of hypovolemia.[1,2,11]

KIDGO AKI classification:[7]

Stage	Serum creatinine	Urine output
1	1.5-1.9 times baseline Or ≥0.3 mg/dl (26.5µmol/L) increase	<0.5ml/kg/h for 6-12 hours
2	2.0- 2.9 times baseline	<0.5ml/kg/h for ≥12h
3	3.0 times baseline OR Increase in serum creatinine to ≥ 4.0 mg/dl (≥353.6 µmol/L) OR Initiation of renal replacement therapy OR, In patients <18 years, decrease in eGFR to <35ml/min per 1.73 m^2	<0.3 ml/kg/h for OR ≥ 12 hours Or Anuria for ≥ 12hours

Study Protocol: All patients of septic shock in ICU included in the study will be resuscitated according to SSC guidelines. Patients with septic shock will initially be resuscitated with crystalloids to maintain a MAP ≥65 mm Hg. The adequacy of fluid resuscitation is monitored by CVP (8-12 mm Hg), PPV (<13%) and PLR test.[1,2] Following adequate resuscitation, if the MAP still remains less than 65 mm Hg then nor-epinephrine will be used as the first line vasopressor.[2] Nor-epinephrine infusion will be started at a dose of 0.05µg/kg/min and gradually increased to 0.2µg/kg/min. Once the mean arterial pressure (MAP) is >65 mm Hg and will be started on dobutamine at a dose of 3µg/kg/min. In case if MAP falls below 65 mm Hg despite the above ionotropic

support, vasopressin will be added as rescue drug in a dose upto 0.03U/min.

The response to vasopressors / ionotropes and resuscitation will be monitored by vital parameters such as heart rate, MAP, CVP, ejection fraction (EF), ScvO2 and urine output. Lactate and RRI will be measured at admission, 1-hr, 6-hrs, 12-hrs, 24-hr and 48-hrs following start of ionotropes. S. Creatinine is measured every day for 72 hours. SOFA score will be measured everyday.

Renal Resistive Index measurements:

Bedside Doppler ultrasonography is performed with a 7.5 MHz transducer, using a previously described RI measurements technique. Using sonography one of the kidneys is identified and interlobar arteries localized using colour Doppler mode. Pulse-wave Doppler will be used to measure blood velocities in the inter-lobar arteries. Peak systolic and end-diastolic velocities will be measured in 3 consecutive pulses. Resistive Index will be calculated as: RI= (peak systolic velocity – end-diastolic velocity)/peak systolic velocity.[21,22] The RI values presented will be average of the 3 measures performed on the 3 consecutive pulses. Normal values are reported between 0.6 and 0.7.[23] A RRI >0.795 predicted AKI with 82% sensitivity and 92% specificity.[14] Hence a RRI of >0.795 will be considered as increased renal resistive index.

Parameters collected at each RRI measurement:

On each RRI measurement, following data will be recorded: HR, systolic, diastolic and mean arterial pressures, vasopressors doses, lactate, central or mixed venous oxygen saturation (SvO2) PPV, CVP and urine output.

Other data: The following data will be recorded:

Age, admission weight, past medical history of any comorbidities, general and systemic examination, hemogram, RFT, S.electrolytes, LFT, Chest X-ray and SOFA score will be recorded.

Statistical Analysis:

Sample size:

A mean sample size: 50 patients.

Data were described in terms of range; mean ±standard deviation (± SD), median, frequencies (number of cases) and relative frequencies (percentages) as appropriate. Comparison of quantitative variables between the study groups was done using Student t-test and Mann Whitney *U* test for independent samples for parametric and non-parametric data respectively. For comparing categorical data, Chi square ($\chi 2$) test was performed and exact test was used when the expected frequency is less than 5. A probability value (*p* value) less than 0.05 was considered statistically significant. All statistical calculations were done using SPSS (Statistical Package for the Social Science) SPSS 21 version statistical program for Microsoft Windows.

7.3 DOES THE STUDY REQUIRE ANY INVESTIGATIONS OR INTERVENTIONS TO BE CONDUCTED ON PATIENTS OR OTHER HUMANS OR ANIMALS? IF SO, PLEASE DESCRIBE BRIEFLY.

Use of ultrasonography for Renal Resistive index measurements, ABG for lactate, Echocardiography for EF.

7.4 HAS ETHICAL CLEARENCE BEEN OBTAINED FROM YOUR INSTITUTION IN CASE OF 7.3?

Attached Herewith

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STUDY PROFORMA:

Informed consent taken S. No:

Name of the Patient Age: Sex:

Ip/Op no: Weight: Height:

Date of admission: Date of admission to ICU:

Address

Religion

Occupation

Diagnosis:

Co-morbid conditions:

General examination

Built and Nourishment

Pallor Cyanosis Clubbing Icterus Edema

Lymphadenopathy

Vitals: Temperature Pulse Blood Pressure

Respiratory Rate Saturation

Systemic Examination

Respiratory System:

Cardiovascular system

Abdomen

Nervous system

Signature of Candidate **Signature of Supervisor**

SOFA Score at admission:

Initial fluid resuscitation:

Parameters measured following fluid resuscitation:

Parameters measured	Before fluid resuscitation	After fluid resuscitation
HR		
BP (MAP)		
CVP		
PPV		
S. LACTATE		
RRI		
Urine Output		
ScvO2		
PLR		

Signature of Candidate

Signature of Supervisor

Measurements from the start of ionotropes:

Time	Ionotrope used	Dose of ionotrope	HR	BP (MAP)	CVP	ScvO2	PPV	S.lact	RRI	Urine output
0-hr										
1-hr										
6-hr										
12-hr										
24-hr										
48-hr										

Fluid balance (previous 24 hrs)

Laboratory Examination

Investigation	Day 1	Day 2	Day 3
Hemoglobin			
TLC			
S.urea/ S.creat			
S.electrolytes			
Chest Xray			

Signature of Candidate **Signature of Supervisor**

USG abdomen:

Serum electrolytes:

Liver function tests:

S. Procalcitonin:

Cultures:

ECG:

2D echocardiography:

Scoring:

SOFA Score	Day 1	Day 2	Day 3
Score			

Signature of Candidate

Signature of Supervisor

INFORMED PATIENT CONSENT

Date: _____

I.....D/o, W/o, S/o..... .....am willing to participate in the study **"EFFECT OF DOBUTAMINE ON RENAL RESISTIVE INDEX IN SEPTIC SHOCK PATIENTS"** The procedure with its complications has been explained to me in local vernacular language. I have fully understood that no special tests and extra expenditure in any form, merely for the purpose of thesis is being carried out. I am free to opt out the study any time without assigning any reason.

....

Signature of the Witness Signature of the patient

Name:

Signature of Candidate **Signature of Supervisor**

मरीज अनुमति फार्म

तिथि _____

मैं _____ पत्नी/पुत्र/पुत्री

_____ निवासी

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इस शोधकार्य **"EFFECT OF DOBUTAMINE ON RENAL RESISTIVE INDEX IN SEPTIC SHOCK PATIENTS"** में भाग लेने के लिए सहमत हूँ। मैं इस शोधकार्य में भाग लेने के लिए अपनी स्वेच्छा से तैयार हूँ। मैं पुष्टि करता/करती हूँ की यह स्वीकृति देने के लिए मुझे कोई आर्थिक प्रलोभन नहीं दिया गया और न ही दबाव डाला गया है। मुझे इस शोधकार्य का उद्देश्य स्पष्ट कर दिया गया है और मुझे यह विश्वास है की यह विज्ञान और मानवता के लाभ के लिए है। मुझे इस शोधकार्य में होने वाले जोखिम के बारे में समझा दिया गया है और मेरी समझ में यह जोखिम बहुत मामुली है।

मैं इस शोधकार्य में भाग लेने के सम्बन्ध में किसी भी समय अपनी अस्वीकृति व्यक्त कर सकता/सकती हूँ और मेरे अस्वीकृति व्यक्त करने का मेरे इलाज पर कोई प्रभाव नहीं पड़ेगा।

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गवाह के हस्ताक्षर रोगी के हस्ताक्षर/अंगूठे का निशान

नाम: नाम:

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अन्वेषक के हस्ताक्षर

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विद्यार्थी के हस्ताक्षर

ਮਰੀਜ਼ ਰਜ਼ਾਮੰਦੀ ਫਾਰਮ

ਮਿਤੀ_____

ਮੈ_____ਪਤਨੀ/ਪੁੱਤਰ/ਪੁੱਤਰੀ_____

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ਵਾਸੀ

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"EFFECT OF DOBUTAMINE ON RENAL RESISTIVE INDEX IN SEPTIC SHOCK PATIENTS" ਤੇ ਚਲ ਰਹੀ ਖੋਜ ਵਿਚ ਹਿੱਸਾ ਲੈਣ ਲਈ ਰਜ਼ਾਮੰਦ ਹਾਂ। ਇਸ ਖੋਜ ਕੰਮ ਵਿਚ ਹਿੱਸਾ ਲੈਣ ਲਈ ਮੈ ਆਪਣੀ ਮਰਜ਼ੀ ਨਾਲ ਤਿਆਰ ਹਾਂ। ਮੈ ਇਹ ਦਸਣਾ ਚਾਹੁੰਦਾ ਹਾਂ/ ਚਾਹੁੰਦੀ ਹਾਂ ਕੇ ਇਹ ਰਜ਼ਾਮੰਦੀ ਦੇਣ ਵਾਸਤੇ ਮੈਨੂ ਕਿਸੇ ਵੀ ਤਰਾਂ ਦਾ ਲੋਭ-ਲਾਲਚ ਨਹੀ ਦਿੱਤਾ ਗਿਆ ਅਤੇ ਨਾ ਹੀ ਕੋਈ ਦਬਾ ਪਾਇਆ ਗਿਆ ਹੈ। ਮੈਨੂ ਇਸ ਖੋਜ ਦਾ ਮਨੋਰਥ ਸਮਝਾ ਦਿੱਤਾ ਗਿਆ ਹੈ ਅਤੇ ਮੈਨੂ ਇਹ ਭਰੋਸਾ ਦਵਾਇਆ ਗਿਆ ਹੈ ਕੇ ਇਹ ਖੋਜ ਵਿਗਿਆਨ ਅਤੇ ਮਾਨਵਤਾ ਦੀ ਭਲਾਈ ਲਈ ਹੈ। ਮੈਨੂ ਇਸ ਖੋਜ ਵਿਚ ਹੋਣ ਵਾਲੇ ਖਤਰੇ ਬਾਰੇ ਸਮਝਾ ਦਿੱਤਾ ਗਿਆ ਹੈ ਅਤੇ ਮੈਨੂ ਇਹ ਯਕੀਨ ਹੈ ਕੇ ਇਹ ਖਤਰਾ ਬਹੁਤ ਮਾਮੂਲੀ ਹੈ। ਮੈਨੂ ਇਸ ਖੋਜ ਕੰਮ ਵਿਚ ਹਿੱਸਾ ਲੈਣ ਦਾ ਢੰਗ – ਤਰੀਕਾ ਸਮਝਾ ਦਿੱਤਾ ਗਿਆ ਹੈ।

ਮੈ ਇਸ ਖੋਜ ਕੰਮ ਵਿਚ ਹਿੱਸਾ ਲੈਣ ਬਾਰੇ ਆਪਣੀ ਰਜ਼ਾਮੰਦੀ ਕਿਸੇ ਵੀ ਸਮੇ ਵਾਪਸ ਲੈ ਸਕਦਾ ਹਾਂ/ ਸਕਦੀ ਹਾਂ ਅਤੇ ਮੇਰੀ ਰਜ਼ਾਮੰਦੀ ਵਾਪਸ ਲੈਣ ਦਾ ਮੇਰੇ ਇਲਾਜ ਤੇ ਕੋਈ ਅਸਰ ਨਹੀ ਹੋਵੇਗਾ।

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ਗਵਾਹ ਦੇ ਹਸਤਾਖਰ ਮਰੀਜ਼ ਦੇ ਹਸਤਾਖਰ

ਮਿਤੀ_____ ਮਿਤੀ_____

ਪਤਾ _____ ਪਤਾ _____

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ਨਿਰੀਖਕ ਦੇ ਹਸਤਾਖਰ

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ਸਿਖਿਆਰਥੀ ਦੇ ਹਸਤਾਖਰ